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Microwave-initiated living free radical polymerization: rapid formation of custom Rasta resins

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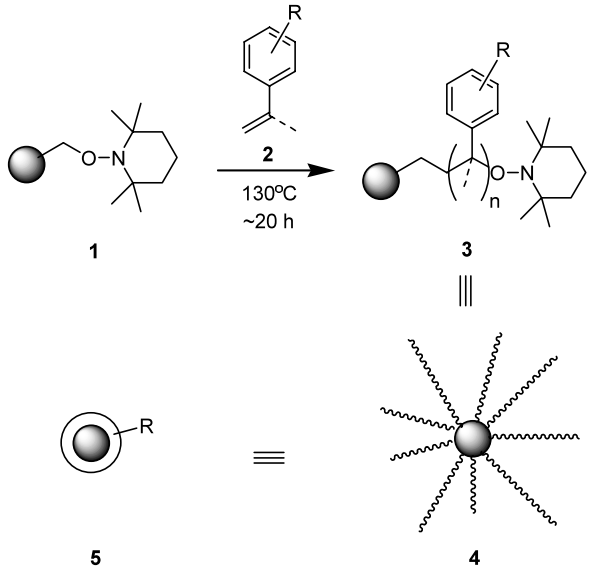
Abstract—Microwave heating of high-loading TEMPO-methyl resin with functionalized styrenyl monomers in a SmithSynthesizer™ affords larger resin beads (>500 μm) via living free radical polymerization. Novel, high-loading Rasta resins (>5.5 mmol/g) are obtained ~150 times faster than with conventional heating.

In several recent reports, Hodges and co-workers have reported on the preparation of designer resins by solid supported living free radical polymerization (LFRP).[1] The LFRP process is initiated by heating TEMPO-methyl resin **1**, a solid-supported radical initiator, with functionalized styrenyl monomers **2** at 130°C for an average of 20 h to deliver high-loading 'Rasta resins' **3**.[1] Scheme 1 illustrates the architecture of a generic Rasta resin depicted by a cartoon structure **4** in which hair-like appendages represent new block polymer growth or alternatively by **5** wherein the shaded inner circle represents the original cross-linked polystyrene (PS) core and the outer clear circle represents new polymer growth. This new class of resins was shown to have unique macromolecular architecture wherein linear block polymers emanate from the original cross-linked PS core. Moreover, by careful selection of co-monomers in the LFRP step, loading capacity, resin physical properties and functional group spacing could be controlled.[1,2]



Scheme 1.

Recently, the literature has seen a plethora of microwave-assisted protocols for chemical transformations.[3] However, microwave technology has not yet been applied to living free radical polymerization strategies in solution or on solid support. As this process is a solvent free suspension polymerization, the low loss tangent (tan δ) of the styrenyl monomers (the 'solvent') was a source of concern as nonpolar molecules are poorly heated under microwave irradiation.[4] However, the issue of energy transfer and heating rates proved not to be a problem. In this letter, our laboratory reports on the first application of microwave technology for solid-supported LFRP and the expedient preparation of novel, high-loading Rasta resins.

Reaction conditions for a microwave-initiated LFRP protocol were quickly developed on a SmithSynthesizer™ to provide Rasta resins with optimal growth (Product/Initiator or P/I ratio), loading and spherical particle size.[5] In the event, **1** (200 mg, 1.86 mol/g, 192 μm, 0.37 mmol) was suspended in *p*-bromostyrene **6** (3.3 mL, 16.8 mmol, 45 molar excess) in a 5 mL Smith

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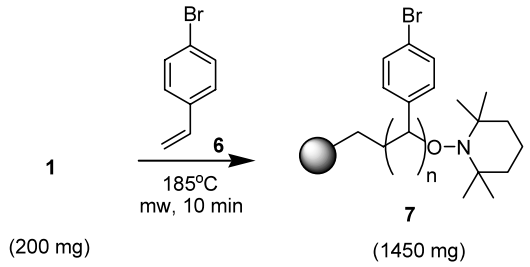
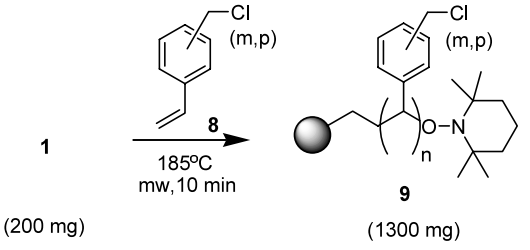


Scheme 2.

Reaction vial at 185°C for 10 min leading to complete solidification of the monomer (Scheme 2). Addition of CH_2Cl_2 to the polymeric mass dissolves remaining **6** as well as any soluble polymer species. Filtration through a sintered-glass frit and washing with five cycles of CH_2Cl_2 and CH_3OH delivered free flowing, spherical resin beads. After overnight drying in a vacuum oven at 50°C, the resin produced, **7**, was visibly larger than the starting **1**, displayed a 7.25-fold increase in mass and bromine analysis (44% Br) indicated a loading level of 5.5 mmol/g.[6] This result is consistent with the conventional thermal data generated for **7**.[1]

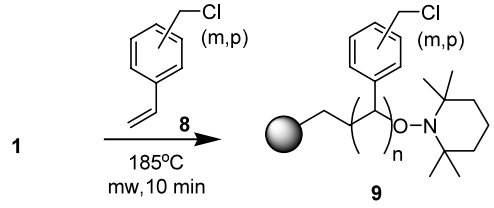
With this proof of concept in hand, our efforts centered on preparing a novel Rasta Merrifield resin in order to access a variety of functionalized Rasta resins for use in solution phase parallel synthesis.[7] Application of our optimal microwave-initiated LFRP conditions employing **1** (200 mg, 1.86 mol/g, 192 μm, 0.37 mmol) suspended in (*m*,*p*-mix)-chloromethylstyrene **8** (2.8 mL, 16.8 mmol, 45 molar excess) in a 5 mL reaction vessel at 185°C for 10 min led to complete solidification of the monomer (Scheme 3). Typical work-up, as described for **7**, provided Rasta Merrifield resin **9**, with a 6.5-fold increase in mass and a loading level of 5.9 mmol/g (20.8% Cl).[6] Consistently, a 6-fold mass increase and a loading of ~5.8 mmol/g (avg. 20.3% Cl) was observed from lot to lot of **9** prepared on the SmithSynthesizer™ (Table 1), demonstrating the reproducibility of this protocol.

Previous work in this arena employed **1** with a particle size of 75–150 μm and a TEMPO loading of ~1.0 mmol/g resulted in Rasta resins that approached 250 μm in diameter. For this work, Argonaut Technologies provided **1** with a uniform particle size of 192 μm as well as a higher loading of 1.86 mmol/g.[8] The resulting Rasta resins were visibly very large and the particle size was quantified by microscopic analysis to be ~550 μm,



Scheme 3.

Table 1. Preparation of Rasta Merrifield resin, **9**



entry	P/I ratio[a]	Analysis(%)	Loading (mmol/g)
1	6.7	C 72.42; H 6.04; N 0.11; Cl 20.50	5.86
2	6.4	C 72.26; H 6.11; N 0.12; Cl 20.18	5.76
3	6.6	C 72.53; H 6.05; N 0.14; Cl 20.24	5.78
4	6.1	C 72.30; H 6.10; N 0.14; Cl 20.60	5.88
5	6.1	C 72.08; H5.93; N 0.09; Cl 20.62	5.90
6	6.2	C 72.22; H 6.00; N 0.19; Cl 20.56	5.87

a: P/I ratio = weight of product bead/weight of initiator bead. 200 mg of **1** employed for each entry.

among the largest PS-based resins described and the largest Rasta resins reported. Figure 1 shows photographs of unswollen **1**, **7**, and **9** at equal magnification with the initial 200 μm diameter indicated.[9] Note, the resins remain spherical in shape.

In general, every functionalized styrene we employed under these standard conditions (185°C, 10 min) afforded optimal growth, loading and spherical particle size except for 4-vinyl pyridine, **10**. For this monomer, optimal conditions proved to require extended heating (40 min) at a lower temperature (170°C). In this instance, suspending **1** (200 mg, 1.86 mol/g, 192 μm, 0.37 mmol) in 4-vinylpyridine **10** (1.83 mL, 16.8 mmol, 45 molar excess) in a 5 mL reaction vessel at 170°C for 40 min led to complete solidification of the monomer (Scheme 4). Typical work-up, as described for **7**, provided Rasta pyridine resin **11**, with a 4.25-fold increase in mass and a loading level of >6 mmol/g.[6,10] Unlike other PS-based pyridine resins, Rasta pyridine **11** not only demonstrated swelling in CH_2Cl_2, DMF and THF but also CH_3OH and other polar solvents. Due to the unexpected swelling properties of **11**, our attentioned next focused on preparing a diverse collection of amine functionalized Ratsa resins for use in solution phase parallel synthesis.

Historically, aminomethyl-PS resins have been prepared by heating Merrifield resin with amines in DMF at 65°C for 6 h.[7] After surveying a number of conditions, a general microwave-accelerated protocol was developed on a SmithSynthesizer™ to quickly deliver aminomethyl-Rasta resins. Heating an excess of 1°- and

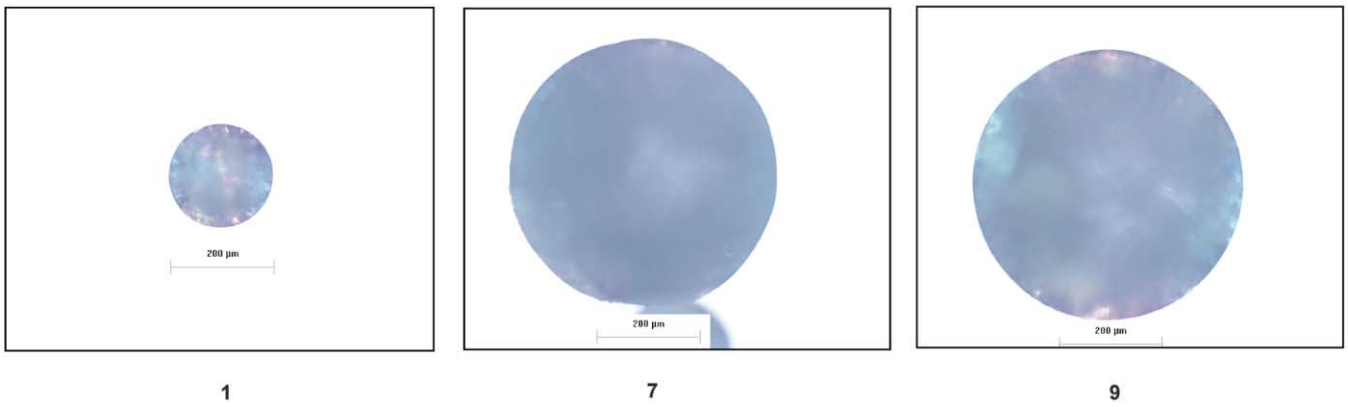
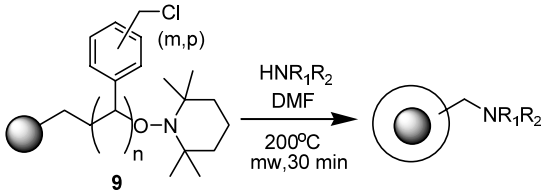
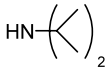
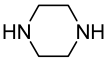
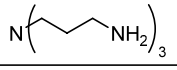


Figure 1. Resin photographs (equal magnification).

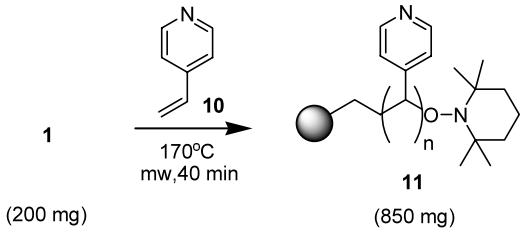
2°-amines with **9** at 200°C for 30 min (Table 2) expediently delivered novel Rasta resins in excess of 500 μm with loading levels of >4.0 mmol/g.[6,11] Representative examples include such important solution phase reagents and scavengers as Rasta-DIEA (entry 2), Rasta-NMM (entry 4), Rasta-piperazine and a Rasta-trisamine congener (entry 6). As with Rasta-pyridine **11**, the resins in Table 2 demonstrate swelling in CH_2Cl_2, DMF, CH_3OH and a number of polar solvents in which their PS-based congeners do not. One explanation for this phenomenon concerns the lack of cross-linking in these new resins.[1,2] Without the 1–2% DVB cross-linking in the new polymer growth, the inherent

Table 2. Preparation of Rasta amines



entry	HNR_1R_2	Analysis (%)	Loading
1	$HNEt_2$	C 82.48; H 6.04 N 7.13; Cl <0.10	5.0 mmol/g
2		C 81.05; H 9.03 N 6.24; Cl <0.27	4.5 mmol/g
3		C 83.00; H9.62 N 7.03; Cl <0.22	5.0 mmol/g
4		C 76.59; H 8.04 N 7.01; Cl <0.19	5.0 mmol/g
5		C 74.25; H 7.50 N 11.7; Cl <0.27	4.2 mmol/g
6		C 72.30; H 7.32 N 17.4; Cl <0.27	4.0 mmol/g

100 mg of **9** employed for each entry in Table 2.

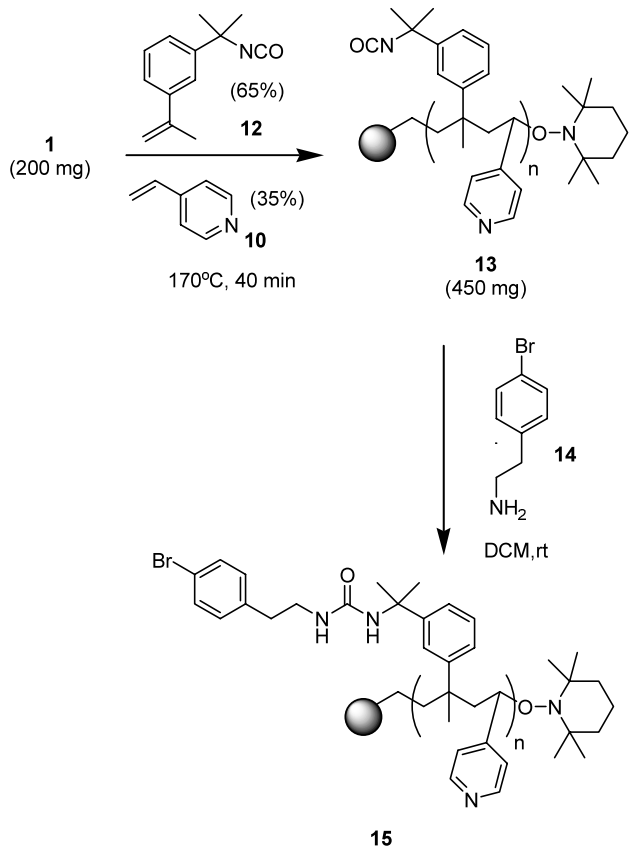


Scheme 4.

polarity of the amine functionality on the linear block polymers may override the hydrophobicity of the PS-core rendering them partially hydrophilic. Studies in this arena are ongoing.

These data also hold great promise for the use of **9** for solid phase organic synthesis (SPOS). Based on the particle size and loading levels obtained by microwave-initiated LFRP of **1** with functionalized styrenes, a *single* bead can be expected to yield >500 nmol of compound—a significant increase over resins reported to date.[12] Moreover, commercial resins offer either a small particle size (75–150 μm) and high-loading (1.5–4 mmol/g) or a large particle size (500 um) and modest loading (0.8–1.2 mmol/g)[13] whereas the Rasta resins reported herein offer both in addition to a macromolecular architecture that affords greater accessibility to pendant functionality.[1,2]

Another significant advantage of Rasta resins concerns the ability to add co-monomers into the polymer feed to customize the loading capacity, distance from the cross-linked PS core, and solvent affinity.[1,2] Based on the unique swelling properties of the Rasta amines, we focused our attention on developing a novel Rasta isocyanate scavenger resin that incorporates a basic amine functionality in the polymer architecture. It was envisioned that a Rasta isocyanate resin of this type would effectively scavenge amines without externally supplied amine base and exhibit better swelling properties. To this end (Scheme 5), **1** (200 mg, 1.86 mmol/g, 0.37 mmol) was suspended in a 45 molar excess of



Scheme 5.

styrenyl monomers consisting of 65% 3-isoproprenyl-α,α-dimethylbenzyl isocyanate (TMI), **12**, (2.3 mL, 10.9 mmol) and 35% **10** (682 μL, 5.73 mol) in a 5 mL Smith Reaction vial for 40 min at 170°C. As observed by Hodges, a solid polymeric mass did not result, but rather the new beads remained suspened in TMI polymer.[1a] Addition of alternating cycles of CH_2Cl_2 and hexanes, followed by drying in a vacuum oven afforded 450 mg (P/I ratio of 2.5) of **13** with a particle size of ~380 μm and a strong isocyanate stretch in the IR spectrum at 2250 cm^{-1}.[14] The loading level of NCO/g was determined by scavenging amine **14**. After typical work-up and drying, elemental analysis of **15** indicated a loading level of 1.6 mmol/g (12.4%Br).[1,6,14] The scavenging reaction proceeded smoothly without additional tertiary amine base and **13** also exhibited swelling in CH_2Cl_2, THF, DMF and CH_3OH.

There does appear to be a significant 'microwave effect' for this LFRP process. Simply increasing the reaction temperature, conventionally, in sealed tubes to 185°C does not deliver Ratsa resins of similar size, loading or uniform shape. Further investigations into the nature of this pronounced 'microwave effect' are underway.

In conclusion, the first application of microwave-initiated living free radical polymerization was reported employing a solid-supported radical initiator to deliver novel Rasta resins ~150 times faster than with conventional heating. This protocol delivered a novel, high-loading (5.8 mmol/g) Rasta Merrifield resin that served as an intermediate for the preparation of a new family of Rasta amine resins for solution phase parallel synthesis with solubility profiles beyond that of their cross-linked PS congeners. Importantly, the particle size of these new Rasta resins approached 550 μm with loading levels in excess of 5.5 mmol/g. These new resins represent the largest and highest loading solid supports reported to date. Clearly, microwave technology holds great promise for the development of novel materials and compositions unattainable under conventional thermal conditions. Additional applications of these new resins for solution and solid phase synthesis and further refinements are in progress and will be reported in due course.

Acknowledgements

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References

1. (a) Hodges, J. C.; Harikrishnan, L. S.; Ault-Justus, S. *J. Comb. Chem.* **2000**, *2*, 80; (b) Lindsley, C. W.; Hodges, J. C.; Filzen, G. F.; Watson, B. M.; Geyer, A. G. *J. Comb. Chem.* **2000**, *2*, 550.
2. McAlpine, S. R.; Lindsley, C. W.; Hodges, J. C.; Leonard, D. M.; Filzen, G. F. *J. Comb. Chem.* **2001**, *3*, 1.
3. For an excellent review, see: Lindstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 925 and references cited therein.
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5. For information on Personal Chemistry's microwave technology and the SmithSynthesizer™, see: http://www.personalchemistry.com
6. C, H, N, Cl, and Br elemental analysis performed by Quantitative Technologies, Inc. PO Box 470 Salem Ind. Park, Bldg. 5, Rt. 22E, Whitehouse, NJ 08888.
7. (a) Booth, J. R.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882; (b) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193.
8. For information on Argonaut Technologies and the TEMPO-methyl resin, **1**, used for this work, see: http://www.argotech.com
9. Particle size determined by Dr. Wei Xu (Pharmaceutical Research & Development, Merck, West Point). Resin beads were mounted dry on a glass cover slip and examined using an Olympus BX51 polarized light microscope with 100× magnification. Resin pictures (all at equal magnification) were taken with an Olympus DP11 microscope digital camera.
10. Elemental analysis for **11**: 77.02% C, 7.14% H, 11.02% N.
11. We are at a loss to explain why elemental analysis indicates <0.27% Cl and the loading of the Rasta amines are not closer to the 5.8 mmol/g loading for the starting

9. This is under investigation. A representative experimental for Table 2 (entry 3): To a 5 mL SmithSynthesizer™ reaction vial (part # 351521) was placed **9** (100 mg, 5.8 mmol/g, 0.58 mmol) in 2 mL of DMF and excess piperidine (822 μL 8.7 mol, 15 equiv.). The reaction vial was then heated in a SmithSynthesizer™ for 30 min at 200°C. After 30 min, the reaction vial was rapidly cooled to 40°C. The contents were then applied to a centered glass fritted funnel, washed with five cycles of CH_2Cl_2 and CH_3OH and dried overnight in a vacuum oven at 60°C. Analytical analysis of a portion of this resin, ground to a fine powder, was determined to be: 83.00% C; 9.62% H, 7.03% N, 0.22% Cl corresponding to a loading level of 5.0 mmol/g.

12. (a) Based on data from Rapp-Polymere. For information, see: http://www.rapp-polymere.com; (b) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Shreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, *3*, 312.
13. Data on commercial resins obtained from: NovaBiochem (http://www.novabiocem.com); Argonaut Technologies (http://www.argotech.com); Rapp-Polymere (http://www.rapp-polymere.com) and Advanced ChemTech (http://www.advancedchemtech.com).
14. Elemental analysis for **13**: 79.84% C; 7.53% H; 7.84% N. Elemental analysis for **15**: 71.2% C; 8.3% H; 6.19% N; 12.4% Br.