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Microwave-initiated living free radical polymerization: optimization of the preparative scale synthesis of Rasta resins

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Abstract—Microwave heating of high-loading TEMPO-methyl resin with functionalized styrenyl monomers in an ADVANCER™ preparative scale microwave synthesizer affords larger resin beads (>375 μm) via living free radical polymerization (LFRP). Unlike homogeneous MAOS reactions, the heterogeneous LFRP reaction is not directly scalable and required significant optimization. Under modified conditions, high-loading Rasta resins (>3.8 mmol/g) are reproducibly obtained in 40–100 g quantities.

Recently, microwave-assisted organic synthesis (MAOS) has had a profound impact on the way organic and medicinal chemists practice organic synthesis in both academic and industrial laboratories.[1–4] Hundreds of manuscripts have been published highlighting accelerated reaction rates, increased yields with diminished side product formation and increased reaction generality as a result of MAOS.[1–5] Indeed, our laboratory relies heavily on MAOS during the lead optimization (LO) phase of drug discovery.[5,6] In the LO phase, we employ single-mode microwave synthesizers wherein temperature is accurately measured by IR and delivers milligram to gram quantities of compound (reaction vessels from 0.2 to 20 mL). A critical issue for the pharmaceutical industry has been one of scale, that is, would medicinal chemistry routes employing MAOS in the lead optimization phase be translatable to MAOS preparative scale routes for development purposes?

In response to this key issue, numerous companies have developed preparative scale microwave synthesizers employing batch, batch flow, or continuous flow paradigms.[7] Early data suggests that there is scalability of MAOS reactions from single-mode to multimode parallel batch reactors.[8] In our hands, we have observed the same direct scalability of homogeneous MAOS reactions employing a Biotage ADVANCER™, a batch multimode microwave synthesizer with a 300 mL reaction cavity.[9] For instance, our laboratory recently reported on an MAOS protocol for the rapid synthesis of diverse 3,5,6-trisubstituted-1,2,4-triazines **3** by the condensation of an acyl hydrazide **1** and a diketone **2** in HOAc with excess NH_4OAc at 180 °C in 5 min (Table 1).[10] Importantly, these conditions provided **3** in the same purity and yield on a 0.05–3.0 mmol scale in a single-mode synthesizer as observed on a 30 mmol scale in the multimode ADVANCER™.[11]

These data led us to investigate the feasibility of a preparative, heterogeneous microwave-initiated living free radical polymerization (LRFP) protocol for the scalable synthesis of Rasta resins. The LFRP process is initiated by heating TEMPO-methyl resin **4**, a solid-supported radical initiator, with functionalized styrenyl monomers **5** conventionally at 130 °C for an average of 20 h or in a single-mode microwave synthesizer for 5 min at 185 °C to deliver high-loading 'Rasta resins' **6**.[12–15] Scheme 1 illustrates the architecture of a generic Rasta resin depicted by a cartoon structure **7** in which hair-like appendages represent new block polymer growth or alternatively by **8**, 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

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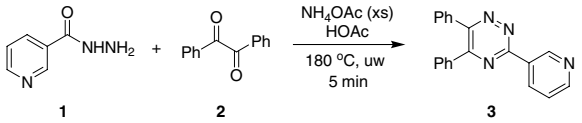
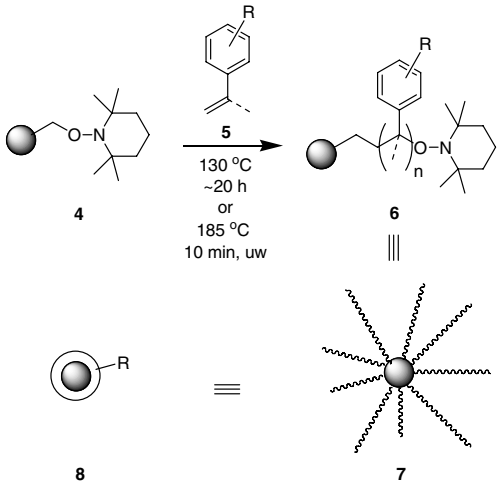
Table 1. Scalable MAOS 1,2,4-triazine synthesis

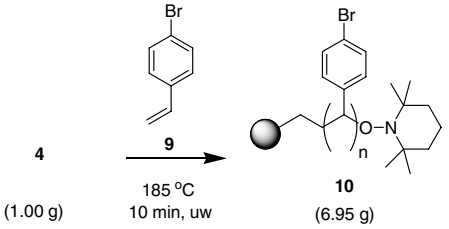


Vial (mL)	Volume (mL)	Amount (mmol)	Theo yield (mg)	Yield (%)	Purity[a] (%)
0.2–0.5	0.25	0.05	15.6	88	86
0.5–2.0	1.00	0.20	62.1	90	92
10–20	10.0	3.00	931.0	92	93
50–300	100.0	30.0	9310.0	92	92

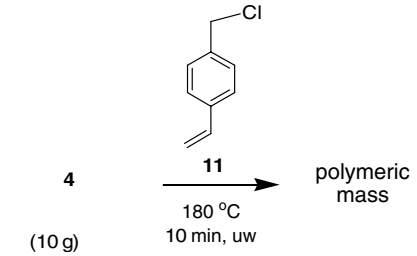
[a] Purity refers to purity of crude reaction by LCMS at 214 nm and ELSD.



Scheme 1. Rasta resin.



Scheme 2. Large scale (20 mL reaction vessel) Optimizer™ run.



Scheme 3. Initial ADVANCER™ run.

macromolecular architecture, wherein linear block polymers emanate from the original cross-linked PS core. In our previous MAOS LRFP protocol, we employed 200 mg of **4** to produce up to 1.5 g (P/I, product/initiator ratios of >6) of various functionalized, >550 μm Rasta resins **6** with loadings in excess of 5 mmol/g. Significantly, there was excellent batch-to-batch reproducibility in the 0.5–2 mL reaction vials.[15] However, even with parallel processing, this protocol provided relatively small quantities of Rasta resins that were insufficient for wide-spread application in our laboratory. Moreover, shortly after our initial report, Aldrich commercialized our Rasta resins ($8–50/g); therefore, the development of a preparative MAOS protocol was of a paramount concern.[16]

Having recently acquired the 20 mL reaction vial capability on our single-mode synthesizer, we examined the MAOS LRFP protocol on a larger scale. As shown in Scheme 2, the scale of the LRFP reaction could be increased 5-fold, such that 1.0 g of **4** would deliver 6.95 g of bromo resin **10** with a P/I ratio of 6.9 and a loading level of 5.2 mmol/g (42% Br) under the same reaction conditions.[17]

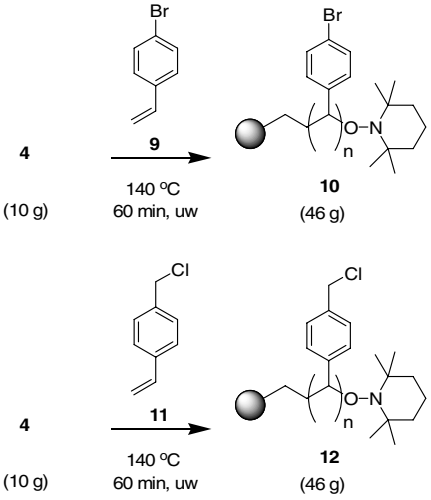
Naively, we anticipated that the LRFP protocol would be directly scalable on the ADVANCER™ system. In the event (Scheme 3), we charged the 300 mL reaction cavity with 10 g of **4** (18.6 mmol, resin loading of 1.86 mmol/g, representing a 50-fold increase over the standard protocol), 35 M equiv of **11** as a solvent, and heated the reaction for 10 min at 180 °C (no stirring and instrument was set to passively cool the reaction). After 2 min of heating, the temperature spiked to above 250 °C and the system underwent a 'crash cool' and shut down. Upon inspection of the cavity after cooling, the LRFP protocol delivered, instead of resin beads, a polymeric mass.

Clearly, the heterogeneous LRFP protocol, unlike the homogeneous 1,2,4-triazine protocol (Table 1), would not be directly scalable. However, there are also instrument differences. First, the LFRP protocol was developed on a single-mode microwave synthesizer, and the ADVANCER™ is a multi-mode microwave. Secondly, the single-mode units measure temperature with IR, while the ADVANCER™ employs a fiber optic thermocouple in the reaction cavity. One explanation for the temperature spike is that the resin polymerized around the thermocouple, thus insulating it from accurately recording the temperature. Only when temperatures exceeded 200 °C, did the resin melt, allowing the thermo-

couple to record the temperature spike. This undesired polymerization and temperature spike was observed at all temperatures examined when using neat styrene as a solvent.

Historically, LFRP is a solvent free suspension polymerization; however, for subsequent experiments, we reduced the temperature and decided to add NMP as a spectator co-solvent.[12–15] Subsequent trials employed 10 g of **4**, a 35 M excess of either **9** or chloromethyl styrene **11**, and 90 mL of NMP (Scheme 4). The reaction was heated at 140 °C for 60 min with a slow ramp of 0.5 °C/s, no stirring and with passive cooling. Under these conditions, the temperature was tightly maintained and there was no temperature spike. The addition of CH_2Cl_2, filtration through a sintered-glass frit and washing with five cycles of CH_2Cl_2 and MeOH delivered free flowing, spherical resin beads **10** and the Rasta Merrifield resin **12**. For **10**, the P/I ratio was 4.6, producing 46 g of resin beads with a loading level of 3.8 mmol/g (30.5% Br) and the P/I ratio for **12** was 4.6, affording 46 g of resin beads with a loading level of 5.30 mmol/g (18.55% Cl).[17] This protocol is reproducible with variations in P/I and loading levels of less than 5% from batch-to-batch. Figure 1 shows the photographs of unswollen **4**, **10**, and **12** at equal magnification, note that the Rasta resins remain spherical, but are smaller (370–450 μm vs >550 μm) than obtained under the original MAOS LFRP protocol.[15,18] While initially disappointing, these beads were found to be more resistant to mechanical breakage than the >550 μm beads while maintaining high-loading levels.

Further optimization studies focused on decreasing the 60 min reaction time and identifying the maximum allowable temperature for LFRP. All temperatures above 160 °C led to temperature spikes, so efforts centered on minimizing the reaction time at 160 °C. As shown in Table 2, 30 min proved to be the optimal reaction time at 160 °C, with diminutions in P/I ratios and loading levels as time decreased. These conditions afforded the same P/I and loading level as those shown in Scheme 4 at 140 °C for 60 min, and afforded an excellent batch-to-batch reproducibility.



Scheme 4.

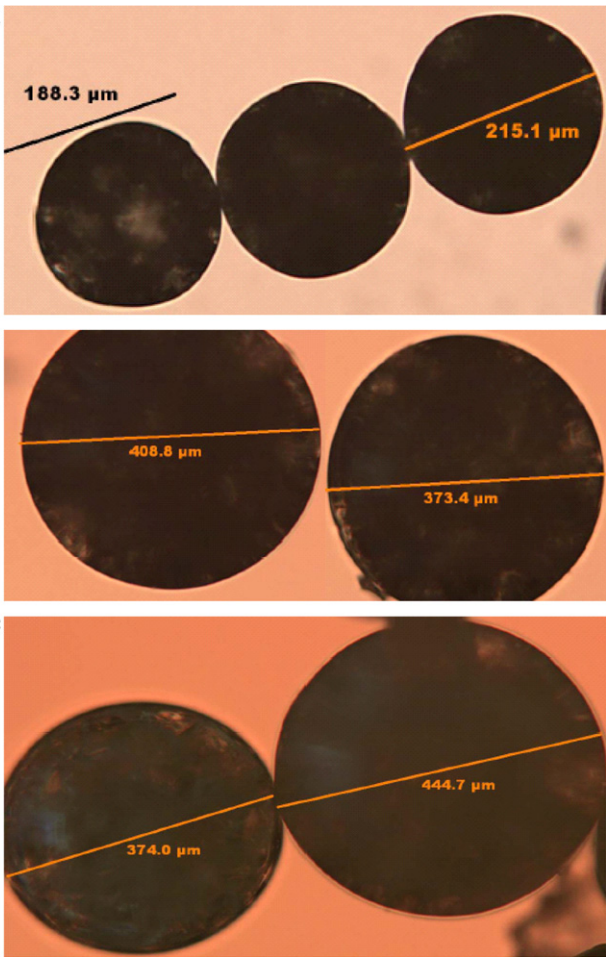
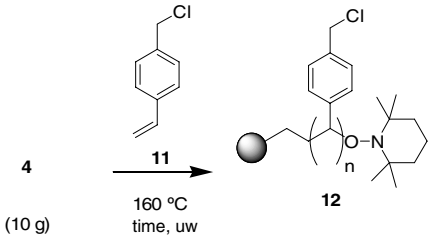


Figure 1. Resin photographs (equal magnification): (a) resin **4**; (b) resin **10**; (c) resin **12**.[18]

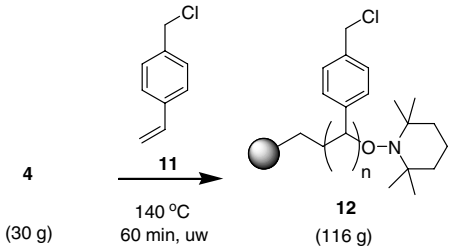
Table 2. Large scale optimization



Time (min)	Resin wt. (g)	P/I ratio	Loading level[a] (mmol/g)
30	41.0	4.1	5.3
15	37.2	3.7	5.4
10	32.6	3.2	5.2
5	28.9	2.9	4.8

[a] Loading based on % Cl; 18.54, 19, 18.3, 16.9, respectively.

Our attention then focused on determining the maximum scale possible in the ADVANCER™ unit. In the event, 30 g of **4** (55.8 mmol, a 3-fold increase of Table 2 and a 150-fold increase in scale over our earlier work)



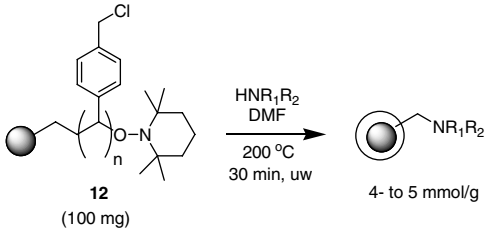
Scheme 5. Large-scale run.

was diluted with a 24 M excess of chloromethyl styrene **11** and 100 mL of NMP (Scheme 5). The reaction was heated at 140 °C for 60 min with a slow ramp of 0.5 °C/s, no stirring and with passive cooling. Under these conditions, the temperature gradually increased to 153 °C then returned to 140 °C within the first 14 min of the reaction, at which then the instrument applied microwave energy to maintain the set temperature.

Upon opening the reaction vessel, a small solid mass was observed in the core of the vessel. This was removed and the remaining resin was washed. The addition of CH_2Cl_2, filtration through a sintered-glass frit, and washing with five cycles of CH_2Cl_2 and MeOH delivered free flowing, spherical Rasta Merrifield resin **12** with a P/I ratio of 3.9, affording 116 g of resin beads with a loading level of 5.30 mmol/g (18.54% Cl).[17]

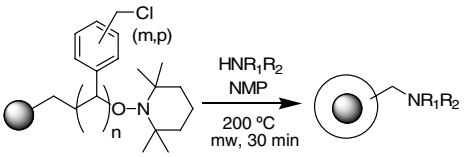
With a scalable synthesis of **12**, efforts centered on scaling up the synthesis of functionalized Rasta resins for use in parallel synthesis. In our earlier work, we were able to generate high-loading (4–5 mmol/g), functionalized Rasta amine resins on ~100 mg scale in the 0.5–2.0 mL reaction vessels (Scheme 6). Once again, this scale was not practical for production and wide-spread adoption in our laboratory. In the ADVANCER™, we increased the scale 100-fold, producing 10 g quantities of functionalized Rasta amine resins (Table 3) with consistent loading levels of 4.5 mmol/g (particle sizes >380 μm) for entries 1–4, and diminished loading for the Rasta piperazine (entry 5) due to internal cross-linking. This directly scalable protocol provided sufficient quantities of such important solution phase reagents as Rasta-DIEA (entry 2), Rasta-NMM (entry 4), and Rasta piperazine (entry 5) for routine solution phase parallel synthesis in the laboratory.

In summary, we have developed a preparative, heterogeneous microwave-initiated living free radical polymerization protocol for the reproducible batch-to-batch synthesis of 40–100 g quantities of Rasta resins with loading levels >3.8 mmol/g and with particle sizes in excess of 380 μm employing a multi-mode ADVANCER™ microwave synthesis unit. Moreover, this study found that not all MAOS reactions are directly scalable, and that heterogeneous reactions benefit from the presence of a spectator solvent. Importantly, this new, scalable protocol finally affords multigram quantities of custom Rasta resins, which should increase the frequency of their application in solid phase and parallel synthesis.



Scheme 6. Rasta amine resins.

Table 3. Large scale synthesis of Rasta amines



Entry	HNR_1R_2	Analysis (%)	Loading (mmol/g)
1	$HNEt_2$	C 82.99; H 9.68; N 6.3; Cl 0.8	4.5
2		C 81.08; H 9.50; N 4.59; Cl 5.07	3.3
3		C 83.56; H 9.62; N 6.31; Cl 0.9	4.5
4		C 77.2; H 8.57; N 6.22; Cl 0.7	4.5
5		C 77.93; H 8.44; N 8.9; Cl 3.2	3.2

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17. C, H, N, Cl, Br analysis provided by Quantitative Technologies Inc., PO Box 470, Salem Ind. Park, Bldg. 5, Rt. 22E, Whitehouse, NJ 08888, USA.
18. The pictures were captured using an Olympus BX51 Polarizing Microscope equipped with an Insight FireWire Color Mosaic Camera. Spot 4.0.5 software was used for picture manipulation.