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LETTERS

Bifunctional Initiators for Free Radical Polymerization of Non-Crosslinked Block Copolymers

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***Abstract*:** Novel bifunctional initiators have been designed with functional groups that independently produce free radicals. Initiators were synthesized to contain both diazene (-N=N-) and 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) moieties tethered by ester or ether linkages. It is anticipated that these compounds will be useful for producing a diverse number of block copolymers for applications in polymer-supported organic synthesis and materials science. © 1998 Elsevier Science Ltd. All rights reserved.

Our lab has been exploring the use of soluble polymer supports in alternative methods to solid-phase synthesis.[1] These methods of liquid-phase synthesis (LPS) employ non-crosslinked polymer supports, such as polyethylene glycol (PEG), that completely dissolve in the reaction medium. However, insolubility in both ether and THF (below room temperature) limit the use of PEG in reactions requiring these solvents. Also, the removal of organometallic reagents and inorganic materials during product isolation is complicated by the solubility of PEG in water. Therefore to accommodate a greater variety of reaction conditions, we are developing non-crosslinked block copolymer supports through the use of bifunctional initiators. The recent publications describing block copolymerization using a sequential normal/living radical polymerization scheme[2-4] have prompted us to disclose our research in this area.

By choosing different monomers and changing block lengths, we envisioned that block copolymers could serve as soluble polymer supports with solubility properties tailored to the designer's needs. Block copolymers are typically made by anionic polymerization; however, a greater number of vinyl monomers are amenable to radical polymerization.[5] Therefore to provide for a diverse set of block copolymers, bifunctional initiators were synthesized with functional groups that independently produce free radicals at two different temperatures. Block copolymers then could be synthesized by heating the initiator and monomer at one temperature, isolating the resulting polymer, and finally heating the polymer with a different monomer at a higher temperature (Figure 1). The ability to isolate the intermediate polymer allows the chemist to determine the solubility properties of the polymer support and "fine tune" macromolecular characteristics through a second polymerization. Thus, bifunctional initiators **1** and **2** were synthesized with both diazene[6] (-N=N-) and 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO)[4,7-9] moieties tethered by an ester or ether linkage to produce soluble polymer supports of different chemical stability.

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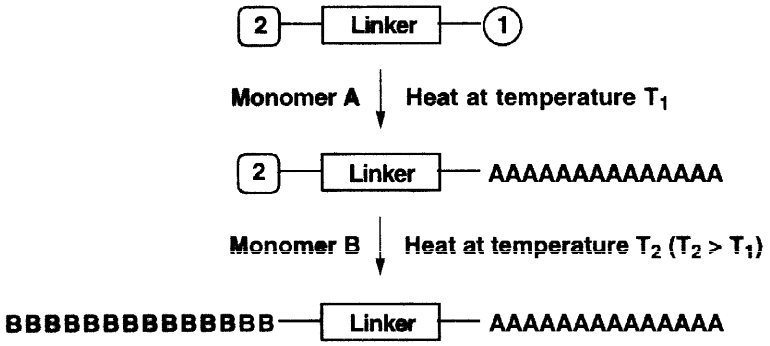
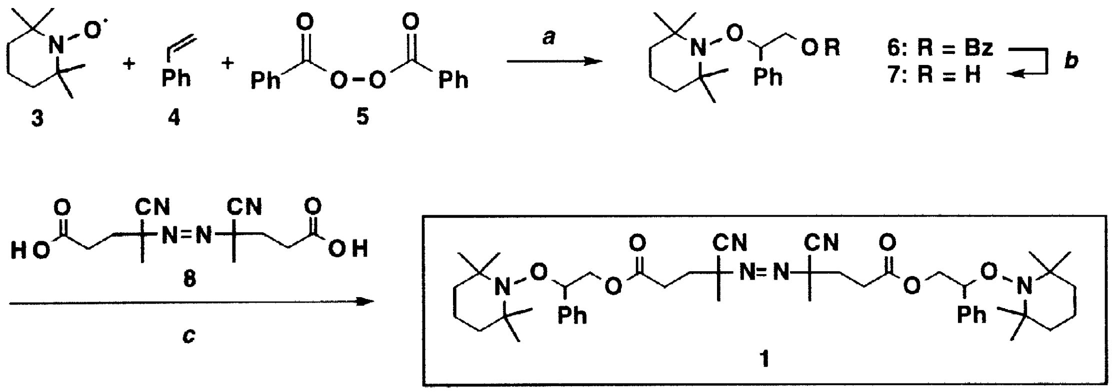


Figure 1. Block copolymerization using bifunctional free radical initiators.

As shown in Schemes 1 and 2, the convergent syntheses of both **1** and **2** share a common TEMPO-containing intermediate (**7**) that was prepared from a modified literature procedure.[8] Benzoyl peroxide (110 g; CAUTION: violently decomposes when heated) was added in portions to a degassed solution of 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO, 50 g) in styrene (525 mL). The temperature of the exothermic reaction was held between 20-30°C by frequent application of an ice bath,[10] and when the exotherm subsided (2 hr), the reaction was heated at 50°C overnight. Cooling the mixture precipitated benzoic acid/benzoyl peroxide which was filtered, pressed, and discarded. The filtrate was concentrated by rotary evaporation and purified by chromatography on silica gel (24:1 hexanes:ethyl acetate). The resulting yellow oil was diluted with an equal volume of methanol and stored in a refrigerator overnight to obtain **6** as a white crystalline solid. The requisite intermediate **7** was obtained in pure form without chromatography through room temperature hydrolysis of **6** using 3:1:1 THF:methanol:10 N NaOH. Based on the most expensive reagent (TEMPO), the overall yield for the synthesis of **7** was twice that previously reported (34 % vs. 16.5%).[8]

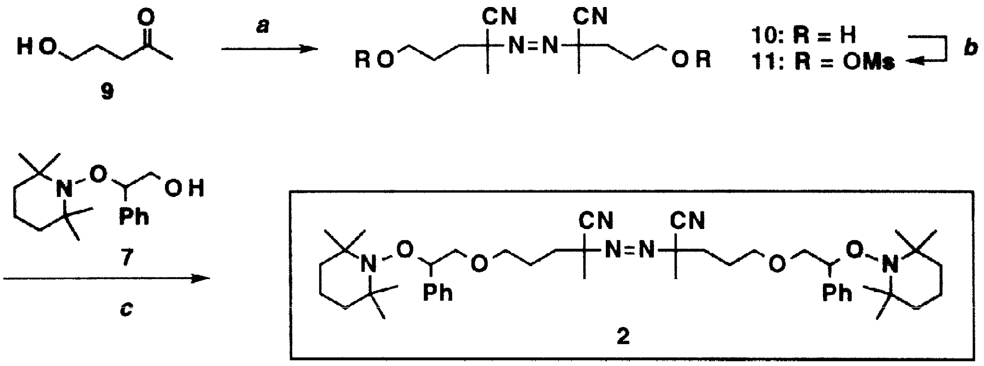
The synthesis of **1** was completed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC)/ hydroxybenzotriazole (HOBT) mediated coupling of **7** with commercially available diazene **8** (Scheme 1). Thus, **1**[11] was obtained in one less step with a higher coupling yield (65%) than the reported procedure[2] using the acid chloride of **8** (28% yield).

Scheme 1



a, 1 equiv. **3**, 15 equiv. **4**, 3 equiv. **5**, <30°C, 2 h, then 50°C, 16 h, 38%; *b*, 12 equiv. NaOH, THF/MeOH/water (3:1:1), 20°C, 16 h, 89%; *c*, 2.05 equiv. **7**, 1 equiv. **8**, 3.6 equiv. EDC, 3.6 equiv. HOBT, DMF, 20°C, 72 h, 65%.

Scheme 2



a, 1.9 equiv. **9**, 1 equiv. hydrazine sulfate, 2 equiv. NaCN, water, 20°C, 72 h, then excess conc. HCl followed by 1 equiv. Br_2 over 4 h, 0°C, 29%; *b*, 3 equiv. MsCl, 3 equiv. NEt_3, CH_2Cl_2, 20°C, 2 h, 95%; *c*, 2.1 equiv. **7**, 2.06 equiv. KH, 2.1 equiv. DMSO, THF, 10 min, 20°C, then transferred to **11** in THF, 90 min, 20°C, 64%.

Soluble polymer supports derived from **1** will contain an ester linkage that may be labile under certain reaction conditions. A copolymer incorporating ester bonds between polymer blocks may be suitable for some applications in materials science;[2] however, we require polymer supports that can withstand a variety of reaction conditions including the use of reagents that might attack the labile ester linkage. Therefore, the need for block copolymers containing the more stable ether linkage motivated the synthesis of **2** (Scheme 2). Although not commercially available, the diazene **10** was synthesized by a one-pot literature procedure.[12] After the mesylate **11** was obtained by standard methods, etherification was successfully performed using KH in DMSO/THF to provide **2**[13] as a pale yellow oil in 64% yield after purification by column chromatography. Surprisingly, no reaction occurred in THF alone.[14]

The bifunctionality of **1** and **2** provides for two independent rounds of polymerization to produce block copolymers in a temperature controlled manner. Preliminary results include the synthesis of several block copolymers by heating **1** or **2** with one monomer at 70°C, isolating and characterizing the resulting polymer, and incubating the TEMPO-containing macromolecule with a different monomer at 130°C. In fact, from a set of 5 different monomers, polymerizations were conducted in parallel using **2** and various monomer combinations in order to synthesize a two-dimensional array of block copolymers. The non-crosslinked soluble supports display a wide range of solubility profiles, and studies are underway to utilize these novel polymer supports in liquid-phase synthesis. These results will be fully disclosed in due course.

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10. The heat of solution released upon dissolving the large amount of BPO in styrene certainly contributed to the observed exotherm. Using a thermometer submerged in the reaction mixture, it was observed that BPO precipitated from solution if allowed to cool below 20°C. When the chilled solution was removed from the ice bath, the reaction temperature soon approached 30°C, and the solution was cooled again.
11. Selected analytical data for **1**: $R_f = 0.25$ [silica gel, hexanes:diethyl ether:ethyl acetate (6:1:1)]; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.33$-7.22 (m, 10H, ArH), 4.93 (t, 2H, $J = 7.9$ Hz, PhCH), 4.62 (m, 2H, PhCHC*H*HO), 4.32 (ABq, 2H, $J = 15.8$ Hz, PhCHCH*H*O), 2.27 (m, 4H, CH_2CO$_2$), 1.60, 1.50, 1.38, 1.32, 1.18, 1.03, 0.68 (each br s, 46H, 8xCH$_2$ and 10xCH$_3$); ^{13}C NMR (CDCl$_3$): $\delta = 17.1$, 20.3, 23.7, 29.0, 32.9, 33.9, 40.3, 60.0, 66.4, 71.7, 83.7, 117.3, 127.5, 127.8, 128.2, 140.2, 170.8; HRMS: calcd for $C_{46}H_{66}N_6O_6$ (M + Cs$^+$) 931.4098, found 931.4115.
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13. Selected analytical data for **2**: $R_f = 0.05$ [silica gel, hexane:diethyl ether:chloroform (8:1:1)]; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.33$-7.22 (m, 10H, ArH), 4.80 (t, 2H, $J = 7.6$ Hz, PhCH), 3.92 (m, 2H, PhCHC*H*HO), 3.58 (m, 2H, PhCHCH*H*O), 3.40 (m, 4H, OCH_2CH$_2$), 1.86 (m, 4H, OCH$_2$CH_2), 1.61, 1.49, 1.36, 1.19, 1.03, 0.64 (each br s, 46H, 8xCH$_2$ and 10xCH$_3$); ^{13}C NMR (CDCl$_3$): $\delta = 17.2$, 20.4, 23.8, 24.5, 33.8, 35.0, 40.5, 59.7, 60.2, 69.8, 72.4, 73.3, 85.2, 85.4, 118.2, 127.3, 127.8, 128.5, 141.9; HRMS: calcd for $C_{46}H_{70}N_6O_4$ (M + Cs$^+$) 903.4513, found 903.4547.
14. Hawker has synthesized ethers from **7** using NaH in refluxing THF.[4,9] However, the final coupling reaction to **2** cannot be heated due to the thermal lability of diazene **11**.