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Reactive & Functional Polymers 68 (2008) 396–405
REACTIVE & FUNCTIONAL POLYMERS
www.elsevier.com/locate/react

Ketone ω-functionalization of polymers prepared by nitroxide-mediated polymerization via addition to a benzyl enol ether

Wilson Chau, Rushia Turner, Rebecca Braslau *

Department of Chemistry and Biochemistry, University of California, Santa Cruz, CA 95064, USA

Received 8 May 2007; received in revised form 15 June 2007; accepted 8 July 2007
Available online 18 July 2007

Abstract

A new method for post-polymerization ω-end-group functionalization of polymers prepared by nitroxide-mediated free radical polymerization (NMP) is presented. Following polymerization, thermolysis in the presence of the enol ether α-benzyloxystyrene results in termination of the polymer with introduction of a phenyl ketone. The ketone group offers the opportunity for further elaboration by hydrazone or oxime formation under mild, physiologically compatible conditions.

Keywords: Nitroxide; Free radical; Telechelic; Polymer functionalization; Ketone

1. Introduction

Living free radical polymerization has proven to be a very useful synthetic tool for the preparation of unique nanoscale structures whose applications range from biology to microelectronics. Controlled "living" radical polymerizations include nitroxide-mediated radical polymerization (NMP) [1], atom transfer radical polymerization (ATRP) [2], and reversible addition fragmentation transfer (RAFT) [3]. These methods are utilized to synthesize controlled polymers with narrow molecular weight distributions and predictable molecular weights. In the case of NMP, the alkoxyamine initiator bears a nitroxide "cap." During polymerization, the "cap" is thermolytically cleaved from the "foot": monomer units are added followed by rapid trapping of the transient polymer radical by the capping agent. The equilibrium between free polymer radical and capped dormant polymer is the key to the highly controlled nature of these radical polymerizations affording low polydispersities (PD) below 1.5. Another advantage of these "living" free radical polymerizations is the ability to grow block copolymers. Macroinitiators composed of an A block can undergo polymerization with a second monomer to form an AB diblock copolymer. As long as the radical "cap" remains intact at the terminus of the polymer chain, multiple blocks can be added sequentially.

There is great interest in the chemo- and regioselective functionalization of the terminus of designed polymer chains for potential applications

* Corresponding author. Tel.: +1 831 459 3087; fax: +1 831 459 2953.
E-mail address: braslau@chemistry.ucsc.edu (R. Braslau).

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doi:10.1016/j.reactfunctpolym.2007.07.006

in drug-delivery and biosensors. One approach is to pre-functionalize the pendant "foot" of the initiator for post-polymerization attachment of various species, such as lipids [4] or proteins [5]. Pre-functionalization ensures complete incorporation of a reactive handle on every polymer, but requires the functionality be able to survive the polymerization conditions. A complimentary approach is to functionalize the opposite ω-terminus of the polymer chain by replacing the cap with a post-polymerization radical trap. This strategy is more general, in that unfunctionalized initiators can be used, but post-polymerization derivatization may not be quantitative. A few examples of post-polymerization derivatization include the work of Georges [6] in which polymers prepared by NMP were modified to incorporate terminal alcohol, ketone and alkyl halide functionalities. Sawamoto [7] has utilized silyl enol ethers to generate ketone-functionalized chain ends using ATRP. Priddy [8] has utilized enol ethers as chain transfer agents in the *uncontrolled* free radical polymerization of styrene to control the molecular weight in addition to functionalizing the terminus of the polymers with a ketone functionality.

The enol ether α-benzyloxystyrene was envisioned as an attractive ω-capping agent for polymers synthesized via NMP. Herein is reported the post-polymerization modification of nitroxide end capped polymers to install a terminal ω-phenyl ketone. Upon heating polymers prepared by NMP with three equivalents of enol ether, homolysis of the nitroxide "cap" generates a transient polymer radical, which adds to the benzyl enol ether. Fragmentation generates a terminal phenyl ketone and a primary benzyl radical. The benzyl radical is trapped by the persistent nitroxide to form the very stable primary alkoxyamine side product (Scheme 1). Ketones offer an orthogonal functional group for biological applications. For example, Bertozzi [9] has demonstrated the versatility of the ketone group in the preparation of glycoprotein mimics via condensation of cell-surface ketones to form hydrazone, oxime and thiosemicarbazones.

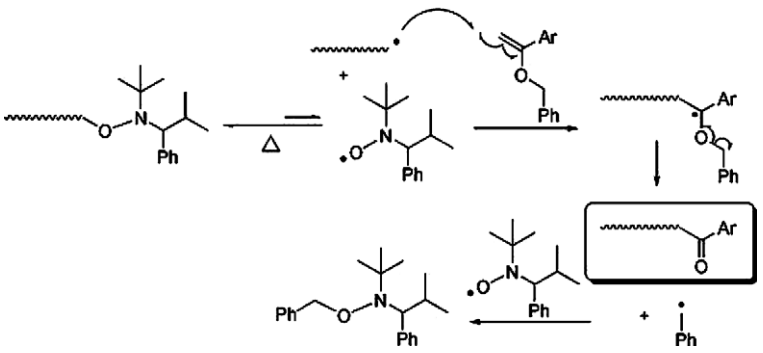
2. Experimental

2.1. Starting materials

Styrene (99.9%, Fisher) and *tert*-butyl acrylate (98%, Aldrich) were distilled under vacuum before use. Dinitrophenylhydrazine (DNP) was recrystallized from acetonitrile. All other reagents and solvents were used as received. Water was deionized.

2.2. Characterization techniques

Flash chromatography was performed on Sorbent Technologies Silica Gel Standard Grade. TLC was visualized with *para*-anisaldehyde (PAA) or as reported. FT-IR spectra were measured with samples dissolved in $CDCl_3$. NMR spectra were recorded at 500 MHz with TMS as an internal standard for proton and the $CDCl_3$ triplet as an internal standard for carbon. Fluorine NMR spectra were recorded at 470 MHz with $CFCl_3$ as an external standard. Mass spectra were obtained on an electrospray ionization time-of-flight (ESITOF) mass spectrometer. Matrix assisted laser desorption ionization time-of-flight (MALDI-ToF) were performed with an Ettan MALDI-ToF/Pro (Amersham Biosciences, Piscataway, NJ) using a matrix of 1,8-dihydroxy-10H-anthracen-9-one (dithranol) and silver trifluoroacetate as an ion source for polystyrene analysis. Gel permeation chromatography (GPC) was performed using a Waters apparatus equipped with five Styragel columns (300 × 4.6 mm^2, 5 μm bead size), HR 0.5 (pore size: 50 Å, 0–1000 Da), HR 1 (pore size: 100 Å, 100–5000 Da),



Scheme 1. Mechanism of ketone chain end-functionalization via addition of α-benzyloxystyrene.