Notes

Meisenheimer Rearrangement of Allyl *N*-Oxides as a Route to Initiators for Nitroxide-Mediated "Living" Free Radical Polymerizations

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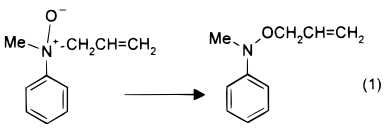
A new method for preparing unimolecular initiators for the "living" free radical polymerization of styrene based on the oxidation and Meisenheimer rearrangement of allylic *N*-oxide derivatives of 2,2,6,6-tetramethylpiperidine has been developed. Such initiators can be used in a nitroxyl-mediated free radical polymerization to prepare well-defined polymers.[1] This nitroxyl-mediated polymerization chemistry along with related atom-transfer polymerization chemistry[2] affords polymers with narrow molecular weight distributions and with control over chain end functionality. Such results were previously achieved only by "living" anionic, cationic, or group transfer methods—chemistry that is limited in the sorts of monomers that can be used.[3−5] These "living" free radical polymerization techniques contrast with other living polymerizations in that these free radical processes can accommodate a broader range of functionality in the substrate monomers.

The original examples of nitroxide-mediated radical polymerization described by Georges attained living behavior in the radical polymerization of styrene by initiation with common initiators such as benzoyl peroxide in the presence of a stable nitroxyl radical like 2,2,6,6,-tetramethyl-1-piperdinyloxy (TEMPO).[1] In these examples, TEMPO serves as a reagent for reversibly trapping the growing polymer chain, thus minimizing radical recombination leading to chain termination. The success in using TEMPO as a reagent in the polymerization of styrene and styrene derivatives consequently has led to the use of TEMPO derivatives as initiators.[6] Hawker's work has emphasized the desirability of unimolecular adducts of TEMPO that act as initiators and contain an inherent 1:1 stoichiometry of initiator and TEMPO. Here we describe an alternative route to such initiators using the Meisenheimer reaction.

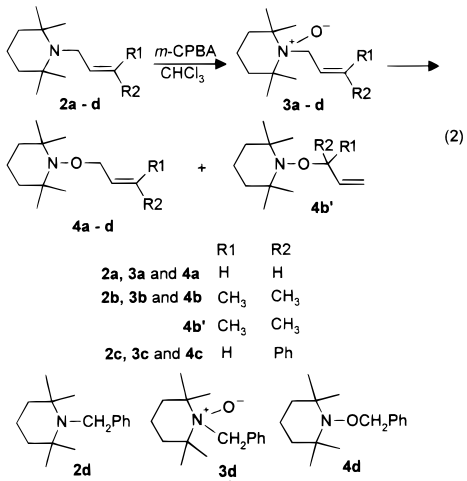
A recent report on the mechanism of the Meisenheimer rearrangement[7] prompted us to investigate this procedure as an alternate route to TEMPO derivatives such as those prepared previously. The Meisenheimer rearrangement shown in eq 1 is a classical organic reaction.[8] Though the mechanism of this reaction is not firmly established (both a concerted sigmatropic rearrangement and a radical process involving radical recombination within a solvent cage are proposed),[9,10] the reaction in eq 1 is a facile route to *N*-(allyloxy)-amines from *N*-oxides of allylic amines.



(1)

To use the Meisenheimer rearrangement to form TEMPO initiators, we needed to first prepare *N*-allyl-substituted 2,2,6,6-tetramethylpiperidine. Oxidation of the resulting tertiary amines would then lead to the allyl-substituted amine oxide substrate for a Meisenheimer rearrangement (Table 1). To accomplish this, we first allylated 2,2,6,6-tetramethylpiperidine. Allyl bromide, prenyl bromide, and cinnamyl bromide (**1a**−**c)** or benzyl bromide (**1d**) was combined with 2,2,6,6-tetramethylpiperdine in dry acetone and refluxed with K_2CO_3 as described by Majumdar to yield the desired *N*-allyl-2,2,6,6-tetramethylpiperidine.[7]

The yields of the allylations varied from 46 to 79% (on the basis of 2,2,6,6-tetramethylpiperdine). The low yields relative to what one might achieve in the allylation of simple amines reflect the poor nucleophilicity of 2,2,6,6-tetramethylpiperdine due to steric crowding around the nitrogen of this hindered amine. Oxidation of the tertiary amines **2a**−**d** with 1 equiv of *m*-CPBA in chloroform at 0 °C resulted in oxidation of the amine to the *N*-oxide, **3a**−**d** (eq 2). No attempt was made to isolate the allylamine *N*-oxide intermediate.



(2)

During the course of addition of *m*-CPBA and subsequent warming of the *N*-oxide solution to room temperature, Meisenheimer rearrangement occurred to form the desired products **4a**−**d**. The rearrangement of **3b** led to the formation of **4b** as well as formation of 10% of the inverted product **4b′** in accord with previous reports on rearrangements of substituted allylic *N*-oxides.[9] We did not detect any inverted product in the

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Table 1. Yields Obtained with and without Oxygen Present during the Rearrangement of *N*-Allyl Derivatives

product	yield in air (%)	yield (degassed)[a] (%)
allyl-TEMPO	59	60
benzyl-TEMPO	21	41
cinnamyl-TEMPO	10	74
prenyl-TEMPO	45	50

[a] The chloroform solutions of the reactants were degassed by three freeze−thaw cycles prior to reaction.

Table 2. Polydispersity of Polystyrene Prepared from Various Allylic Amine Oxide Initiators

initiator	PDI of polystyrene	initiator	PDI of polystyrene
allyl-TEMPO (**4a**)	1.19	cinnamyl-TEMPO (**4c**)	1.21
prenyl-TEMPO (**4b**)	1.29	benzyl-TEMPO (**4d**)	2.81

case of the cinnamyl derivative. The crude product from these oxidation reactions was a reddish oil that had a menthol-like odor similar to that of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical. Purification of the crude product by column chromatography over silica gel with 6:1 hexanes:ethyl acetate, as eluent yielded the desired TEMPO derivative along with tertiary amine, aldehyde, and free TEMPO, which was responsible for the red color and odor of the crude product. The low yields of the benzyl and cinnamyl derivative were thought to arise from a radical recombination mechanism in which oxygen was participating in the reaction.[10] To test this hypothesis, the oxidation and Meisenheimer rearrangement were repeated for each of the tertiary amines **2a**−**d** with precautions taken to exclude oxygen in the reaction system. The chloroform solution of the tertiary amine and the *m*-CPBA solutions were degassed under an argon atmosphere using three freeze−thaw cycles. The exclusion of oxygen led to increased yields of the desired products in the case of the benzyl and the cinnamyl−TEMPO derivatives.

In a typical procedure, 1 g of 2,2,6,6-tetramethylpiperidine, 1 equiv of the desired halide and 1 g of K_2CO_3 were allowed to reflux in acetone for 12 h. The *N*-allyl 2,2,6,6-tetramethylpiperdine product was then isolated and purified by column chromatography. Oxidation was accomplished by dropwise addition of *m*-CPBA over 20 min with 1 equiv of *m*-CPBA in $CHCl_3$ at 0 °C. After stirring at room temperature for 12 h, the product was isolated by chromatography over silica gel using 6:1 hexanes:ethyl acetate. Styrene polymerizations were carried out with the purified initiators using the literature procedure.[6] The allylic-TEMPO products, **4a**−**d** and the precursor 3° allylic amines **2a**−**d** were characterized by ^{1}H and ^{13}C NMR spectroscopy. High-resolution mass spectrometry (HRMS) was used to confirm the elemental composition of **4a**−**d**. Each HRMS showed the expected molecular ion peak as well as large peaks associated with TEMPO and the respective allyl fragment.

The utility of the purified allyl-TEMPO derivatives as initiators in styrene polymerization was investigated by combining a portion of the unimolecular initiator and distilled styrene in a round-bottomed flask under an argon atmosphere. The solution was immersed in an oil bath at 125 °C and allowed to react for 72 h. The polymerizations were shown to yield polymer with a polydispersity of approximately 1.2 (Table 2). Aliquots taken from the polymerization reaction throughout the course of the polymerization showed that this dispersity number was constant throughout the duration of the polymerization.

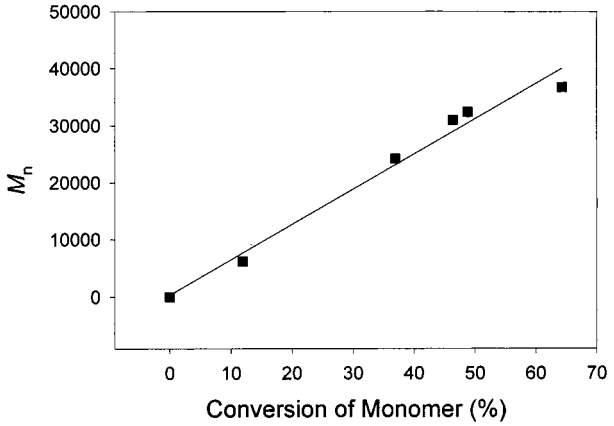

Figure 1. Plot of M_n versus monomer conversion for styrene polymerization initiated by **4c**.

This polydispersity is below the theoretical limit of 1.5 for normal free radical polymerizations and is comparable to the dispersity reported by Georges for a benzoyl peroxide/TEMPO initiated styrene polymerization.[1] Aliquots were taken at selected intervals, and the molecular weight was analyzed by GPC without reprecipitation or other means of fractionation or purification.

The GPC molecular weights also corresponded well to those predicted by molar amounts of initiator and monomer. Doubling the amount of initiator reduced the molecular weight by half. The one exception to polymerization leading to low dispersity polystyrene was the polymerization initiated by benzyl-TEMPO. In this case, polymerization yielded polystyrene having a polydispersity of 2.8. This value was similar to that reported by Hawker for the same initiator molecule.[6] Hawker was able to show that the high polydispersity was a function of the rate at which the benzyl-TEMPO initiator cleavage occurred.

A plot of the molecular weight of the polymer vs percent monomer conversion is shown in Figure 1 for a styrene polymerization. The linear behavior seen is characteristic of these living radical polymerizations.

^{1}H NMR spectroscopy end group analysis of the polystyrene product formed using **4a** as an initiator showed peaks in the δ 3.8−4.2 region expected for *O*-substituted benzyl chain ends. In addition, peaks due to TEMPO were seen in the δ 0.1−1.0 region typical of TEMPO mediated polymerizations. Vinyl end groups in the region δ 4.8−6 were also seen in the ^{1}H NMR spectra of ca. 2000 and 35 000 Da oligomers and polymer. We had expected that the end group derived from the allyl portion of the initiators **4a**−**d** would not be present on the basis of the likely cyclization of the intermediate 6-alkenyl radicals. Comparison of the rate constants for a 7-*endo*- ($k_{cyclization} = 1.9 \times 10^3$ s^{-1} at 65 °C)[11] or a 6-*exo*-cyclization ($k_{cyclization} = 1.1 \times 10^4$ s^{-1} at 65 °C)[11] of a 6-heptenyl radical with the reported rate constants for propagation of styrene ($k_p = 4.8 \times 10^2$ L/(mol·s) at 67.5 °C)[12] had led us to believe that cyclization to form 1,2,4-trisubstituted cyclohexyl and 1,3,5-trisubstituted cycloheptyl end groups should have occurred when **4a** was used as an initiator. However, this evidently does not occur. We speculate that this may reflect differences in cyclization rates for styryl radicals versus 1° alkyl radicals. In any case, a recent

report on ATRP by Nakagawa and Matyjaszewski using allyl halides and copper(I) bromide also indicates vinyl end groups persist in an ATRP polymerization of styrene, supporting our spectroscopic results in the case of polymerizations initiated by **4a**.[13]

In summary, *N*-allyl derivatives of 2,2,6,6-tetramethylpiperdine can be oxidized to the corresponding *N*-oxide by treatment with *m*-CPBA. This product spontaneously rearranges under the reaction conditions yielding the *O*-allyl TEMPO derivative. The TEMPO derivative can then serve as a unimolecular initiator for TEMPO-mediated living free radical polymerizations of styrene.

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Supporting Information Available: Details of experimental procedures (2 pages). Ordering information is given on any current masthead page.

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