

Simple and Efficient Synthesis of Various Alkoxyamines for Stable Free Radical Polymerization

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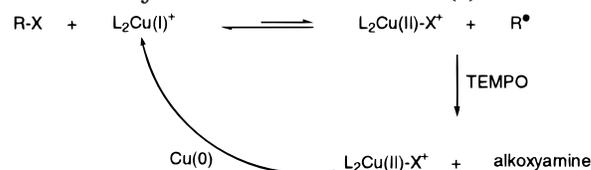
The development of controlled/"living" radical polymerizations has been a field of intensive research in recent years. Much work has been devoted to the development of nitroxide-mediated stable free radical polymerization (SFRP) as a route to prepare well-defined polymers. This process utilizes the ability of the stable nitroxide radical to reversibly bind with an organic radical to form an alkoxyamine as the dormant species in situ. Originally, polymerization has been initiated with a classical free-radical initiator, and the reversible formation and homolytic cleavage of an alkyl–oxygen bond between the growing radical chain and the nitroxide allows for a controlled/"living" polymerization.^{1–3} Later works have successfully employed alkoxyamines prepared in advance as unimolecular initiators for SFRP.^{4–8} Using alkoxyamines as initiators has the advantage of a set stoichiometry between the organic initiator and the nitroxide radical, while in classical free radical initiated SFRP typically a ratio of initiator:nitroxide of 1:1.3 is used in order to account for the low initiator efficiency. The nature of the organic moiety in the alkoxyamines may be tailored to aid the polymerization of several vinyl monomers; therefore, the synthesis of several alkoxyamines has been the subject of recent publications.^{4–8} Notably, Braslau has reported low-temperature multistep synthesis of a variety of alkoxyamine initiators.⁸

Here we report the synthesis of several alkoxyamines derived from organic halides and TEMPO or TEMPO derivatives. If the Cu(0) systems developed in atom transfer radical polymerization (ATRP) are used,⁹ alkoxyamines bearing different functional groups have been prepared in high yield in one simple step. Alkoxyamines with TEMPO coupled to acrylate, methacrylate, and acrylonitrile moieties have been synthesized. Evaluation of initiator efficiency of these alkoxyamines in the polymerization of styrene may allow insight into the effect of the initiator structural variations on polymerization.

Halogen transfer between organic halides and Cu(I) complexes yield copper(II) complexes and organic radicals which are quickly trapped by the nitroxide radicals to form the alkoxyamines. In absence of Cu(0), the copper(II) halide complex builds in concentration as the reaction proceeds and shifts the equilibrium such that complete conversion of the organic halide does not occur.¹⁰ The use of a large amount of Cu(I) complex (in excess over the alkyl halide) and the incomplete conversion made this method impractical for the synthesis of alkoxyamines.

We have recently reported an improvement in ATRP by taking advantage of the ability of copper(0) powder

Scheme 1. Mechanism for Synthesis of Alkoxyamine by ATRA in Presence of Cu(0)



to reduce copper(II) to copper(I) when there are stabilizing ligands present such as dipyriddy derivatives.⁹ This approach can be adapted to allow for the efficient synthesis of a variety of alkoxyamines through the continuous regeneration of the copper(I) complexes by the reduction of the resulting Cu(II)–X (X = halogen) complexes by copper(0) powder. In fact, one can begin with Cu(II) complexes which, in the presence of coordinating ligands and Cu(0), will form Cu(I) complexes in situ to react with the organic halides. The ligands are necessary to solubilize the copper salts and to tune for the appropriate halogen transfer reactivity. Only catalytic amounts of the copper salts and ligand are needed in the reaction. However, copper(0) must be present in excess relative to the organic halide in order for the reaction to go to completion, and a slight excess of the nitroxide trap is usually used to minimize homocoupling of the organic radicals.

Due to the presence of the nitroxide trap and the low concentration of organic radicals, there is little homocoupling of the organic radicals and complete conversion of the organic halide is realized. The reaction is extremely clean with no detectable side products evident in ¹H NMR spectra. For example, to prepare 1-(2,2,6,6-tetramethylpiperidinyloxy)-1-phenylethane (**1**), 1-phenylethyl bromide, Cu^{II}(OTf)₂, 4,4'-*tert*-butyl-2,2'-bipyridine (dTbpy), Cu(0), and TEMPO in a ratio of 100:1:4:105:120 were placed in an NMR tube and diluted with C₆D₆. The ¹H NMR spectrum of the reaction mixture before heating is shown in Figure 1A. After 4 h at 75 °C, the spectrum of the reaction mixture shows nearly complete conversion of 1-phenylethyl bromide to alkoxyamine **1** as indicated by the disappearance of the signals of methine proton and methyl protons at 4.85 and 1.75 ppm and appearance of the signals at 4.92 and 1.57 ppm, respectively (Figure 1B). The spectrum shows no significant side product present.

A variety of alkoxyamines were prepared using this simple and effective method as shown in Table 1.¹¹ The compounds were purified by passing through an alumina (neutral) column to remove the copper complexes and excess nitroxide. The final products were characterized by ¹H NMR, ¹³C NMR, and mass spectrometry. The alkoxyamines were isolated in high yields (70–95%) with complete conversion of the alkyl halides. The synthesis of alkoxyamines by ATRA in the presence of Cu(0) is a versatile method to prepare alkoxyamines bearing different functionalities due to the easy accessibility of various alkyl halides and the high tolerance to functional groups by radical process. Similarly, other metals such as Fe(0)/Fe(II) have been used successfully. Substituted TEMPO can be used as the radical trap. For example, 1-(2,2,6,6-tetramethyl-4-hydroxypiperidinyloxy)-1-phenylethane, **6**, was prepared by coupling 4-hydroxy-TEMPO with the radical derived from 1-phenylethyl bromide.

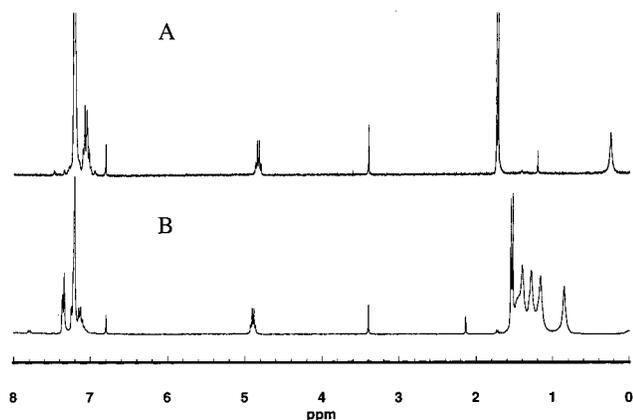


Figure 1. (A) ^1H NMR spectrum of the reaction mixture of 1-PEBr, TEMPO, $\text{Cu}(\text{OTf})_2$, dTbpy, and $\text{Cu}(0)$ in a ratio of 100:120:1:4:105 in C_6D_6 before reaction. (B) ^1H NMR spectrum of the reaction mixture of 1-PEBr, TEMPO, $\text{Cu}(\text{OTf})_2$, dTbpy, and $\text{Cu}(0)$ in a ratio of 100:120:1:4:105 in C_6D_6 after heating for 4 h at 80°C .

Table 1. Synthesis of Alkoxyamines from Alkyl Bromides and Nitroxides in Benzene Solution^a

Alkoxyamine	Compound label	R-X	T ($^\circ\text{C}$)	Time (h)	Yield (purified)
	1		75	4	94
	2		75	12	96
	3		75	12	75
	4		55	18	92
	5		75	8	76
	6		75	5	72

^a RX/nitroxide/ $\text{Cu}(0)/\text{Cu}(\text{OTf})_2/\text{dTbpy} = 100/120/105/1/4$. ^b 4-hydroxyl-TEMPO was used as the radical trap.

Bulk polymerization of styrene was carried out at 125°C to examine the effect of structural variations on the efficiency of these alkoxyamines as initiators in nitroxide-mediated stable free radical polymerization.¹² The results are shown in Table 2. Similar to previous reports,^{5e} ethylbenzene-TEMPO derivatives, such as **1**, were used successfully as unimolecular initiators for SFRP of styrene to afford polymers with predicted molecular weight and low polydispersity (entry 1), while benzyl-TEMPO derivatives, such as ((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methylbenzene (**2**) resulted in polymers with a broader molecular weight distribution. This

Table 2. Bulk Polymerization of Styrene Initiated by Alkoxyamines^a

Entry	Initiator	Time (h)	Conversion (%)	$M_{n,th}$	$M_{n,exp}$	M_w/M_n
1		12	49	9800	6240	1.40
2		12	55	10980	10420	2.85
3		12	22	4380	3140	2.45
4		12	45	9020	8330	1.29
5		12	38	7500	6120	1.29
6	no initiator	12	58		231500	1.68

^a Alkoxyamine/styrene = 1/192, 12 h at 125°C in bulk.

was attributed to slow initiation by benzyl-TEMPO derivatives.^{5e} Interesting results were observed in the case of alkoxyamine ester derivatives. The tertiary-TEMPO derivative ethyl 2-(2,2,6,6-tetramethylpiperidin-1-yl)oxyisobutyrate (**4**) afforded a well-controlled polymerization of styrene with narrow polydispersity, while the secondary-TEMPO derivative methyl 2-(2,2,6,6-tetramethylpiperidin-1-yl)oxypropionate (**3**) provided polymers with broader molecular weight distributions (entries 3 and 4). This result can be correlated with the difficulty in the control of SFRP of acrylates in the presence of TEMPO and the preparation of the corresponding block copolymers.¹³ On the other hand, both the tertiary alkoxyamine with an α -CN substituent, reported by Hawker et al.,^{5e} and the secondary derivative, 2-(2,2,6,6-tetramethylpiperidin-1-yl)oxypropionitrile (**5**), afforded well-controlled polymerization with predicted molecular weight and low polydispersity (entry 5). The ability of **1**, **4**, and **5** to function as initiators for SFRP of styrene providing well-controlled polymerization indicates that all these initiators are consumed in the early stages of polymerization. Structurally, **1**, **3**, **4**, and **5** mimic the dormant species in TEMPO-mediated polymerization of styrene, methyl acrylate (MA), methyl methacrylate (MMA) and acrylonitrile (AN). The results with **1**, **3**, **4**, and **5** as initiators for polymerization of styrene might shed some light on TEMPO-mediated SFRP of MA, MMA, and AN, in particular, the cross-propagation step in the attempted block copolymer synthesis.

In conclusion, a simple and versatile method involving halogen abstraction in the presence of $\text{Cu}(0)$ has been developed to prepare alkoxyamines with different structures and functional groups in one step. The reaction is very selective and easy to workup. Alkoxyamines are typically isolated in 70–95% yield. Alkoxyamines with structures resembling the dormant species of methyl

acrylate, methyl methacrylate, and acrylonitrile have been prepared and used as initiators for TEMPO-mediated stable free radical polymerization of styrene.

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Supporting Information Available: Text giving a detailed synthesis of compounds 2–6 and the characterizations (3 pages). See any current masthead page for ordering and Internet access information.

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- (11) Synthesis of alkoxyamines: All reactions were performed in a similar manner varying only in reaction times and temperatures. As a representative example, 0.50 mL (3.7 mmol) of 1-phenylethyl bromide was added to a Schlenk flask with 0.69 g (4.4 mmol) of TEMPO, 0.24 g (3.8 mmol) of copper powder, 0.013 g (0.037 mmol) of Cu(OTf)₂ and 0.040 g (0.15 mmol) of dTbpy. (Alternatively, CuBr₂ and pentamethyldiethylenetriamine (PMDETA) can be used as the catalyst system.) Benzene, 5 mL, was then added as solvent, and the solution was degassed by three freeze–pump–thaw cycles. The solution was heated to 75 °C with stirring. After 4 h, all the copper powder was consumed and a beige precipitate was formed. The reaction solution was loaded onto an alumina column and eluted with hexanes. The eluent strength was increased to 9:1 hexanes:CH₂Cl₂. The alkoxyamine eluted before TEMPO and was collected as a colorless fraction. The solvent was removed to yield 1-(2,2,6,6-tetramethylpiperidinyloxy)-1-phenylethane (**1**) as a colorless oil. After this oil was stored overnight in a freezer, white crystals formed and were collected, yielding 0.90 g (3.4 mmol) of **1**. Isolated yield = 94%. ¹H NMR: CDCl₃ (δ vs TMS): δ 7.3–7.1 ppm, m, 5H (ArH); 4.78 ppm, q, ³J_{HH} = 7 Hz, 1H (ArCHCH₃O); 1.48 ppm, d, ³J_{HH} = 7 Hz, 3H (ArCHCH₃O); 1.25, 1.14, 1.02, 0.65, each a broad singlet, 12H (TEMPO methyls); 1.6–1.2, m, 6H (TEMPO methyl- enes). See Table 1 for reaction times, temperatures, and yields for the alkoxyamines synthesized by this method.
- (12) Polymerization of styrene: Styrene was distilled over CaH₂ and stored at –5 °C under argon prior to use. In a typical polymerization, a long dry glass tube was charged with initiator (0.045 mmol), styrene (1 mL, 8.7 mmol), and a magnetic stir bar. The glass tube was degassed via three freeze–pump–thaw cycles, and sealed by flame. The glass tube was immersed in an oil bath thermostated at 125 °C. After 12 h, the glass tube was removed and broken. The sample was dissolved in THF, and the conversion (GC) and molecular weight and polydispersity (SEC) were measured.
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