High-Yield Synthesis of Alkoxyamine Initiators Carrying a Functional Group by Reaction of Ethylbenzenes with Di-*tert*-butyl Diperoxalate in the Presence of Nitroxides

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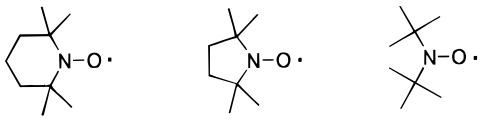
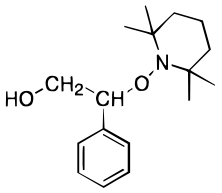
Introduction. Stable free radical (SFR) mediated polymerization has attracted growing attention recently because it allows the preparation of narrow polydispersity (M_w/M_n < 1.3) polymers, which are difficult to obtain by conventional radical polymerization. SFR-mediated polymerization has also been utilized to make a variety of well-defined block and graft copolymers, including star and dendritic polymers, which are difficult to make by other methods.[1−4] Nitroxides including 2,2,6,6-tetramethylpiperidinyl-1-oxyl (**1a**, TEMPO), 2,2,5,5-tetramethylpyrrolidinyl-1-oxyl (**1b**), and di-*tert*-butyl nitroxide (**1c**) are typical SFR that are too stable



1a (TEMPO) **1b** **1c**

to initiate polymerization. After the pioneering work of Rizzardo and Moad,[5] subsequent developments[6,7] in the area of nitroxide SFR-mediated polymerization have shown that the key initiators are alkoxyamines whose C−O bonds are thermally labile, cleaving homolytically at temperatures usually above 100 °C to give a nitroxide and carbon-centered radicals. The carbon-centered radical initiates radical polymerization; after addition of monomers, the growing radical is captured by the nitroxide. Repeating of this cycle (the C−O bond dissociation of the alkoxyamines, addition of monomers, and recombination) controls the polymerization, yielding growing polymer chains with a low polydispersity.

The preparation of alkoxyamines has widely been studied, and many procedures based on the radical trapping technique[8−12] or neucleophilic method[9,13] have been developed in recent years. Alkoxyamines carrying a functional group such as aldehyde and ester can be used to conduct controlled macromolecular architectures by combination of "living" free radical polymerization and other types of polymerization (e.g., anionic and cationic) using functionalized alkoxyamines. Hawker et al. reported the synthesis of a functionalized alkoxyamine **2** by hydrolysis of the benzoyloxy−styrene−TEMPO adduct.[9] A variety of controlled macromolecular architectures have been prepared using **2**.[3] However, it is difficult to synthesize alkoxyamines with a variety of functional groups from **2**. It is therefore important to establish convenient and widely applicable synthetic routes for functionalized alkoxyamines. We have examined several methods for preparation of alkoxyamines and have found that the reaction of



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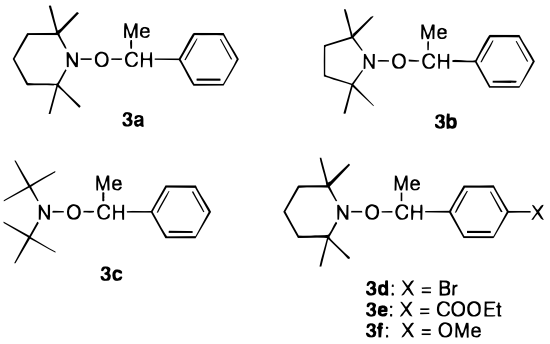
ethylbenzenes with di-*tert*-butyl diperoxalate (**4**) in the presence of nitroxides at 35 °C gives alkoxyamines including 4-bromo (**3d**), 4-ethoxycarbonyl (**3e**), and 4-methoxy derivatives (**3f**) in good yields.[14] Of particu-



lar interest is **3d**, from which a variety of functionalized alkoxyamines can be derived via the corresponding lithio or Grignard reagent. In fact, 4-formyl (**3h**) and 4-hydroxymethyl derivatives (**3i**) were derived from **3d** in high yields. Herein we report the synthesis of functionalized alkoxyamines by reaction of ethylbenzene derivatives with **4** in the presence of nitroxides and conversion from **3d** to **3h** and **3i**.

Results and Discussion. The preparation of **3a** is outlined in Scheme 1. Perester **4** decomposes at a moderate rate in hydrocarbon solvents such as benzene at room temperature to give two *tert*-butoxyl radicals.[15] Since the homolytic decomposition is very clean, **4** has served as a good source of *tert*-butoxyl radicals under mild conditions. This perester can be stored in a freezer (−20 °C) for at least 1 year without decomposition. Therefore, it is not necessary to prepare it each time in preparation of alkoxyamines.

The reaction of ethylbenzene with **4** in the presence of TEMPO was carried out at 35 °C in benzene under nitrogen using 1.0 equiv of **4** for TEMPO and using ethylbenzene as the solvent. When the reaction mixture was stirred for ca. 3 h, the characteristic red color due to the TEMPO radical disappeared, and the solution showed a pale yellow color. After an excess of ethylbenzene was removed at room temperature under reduced pressure, the residue was chromatographed on silica gel to give almost pure **3a** in 90% yield (based on TEMPO).[16] Crystallization from pentane or ethanol gave pure needles with 44−45 °C (lit.[8] 44.5−45 °C).[16] In the same manner the reaction of ethylbenzene with **4** in the presence of **1b** or **1c** was carried out, and alkoxyamines **3b** and **3c** were obtained in 89 and 90% yields, respectively, as a colorless oil after column chromatography. Identification of **3b** and **3c** was accomplished by the ^{1}H NMR spectra.[17,18]

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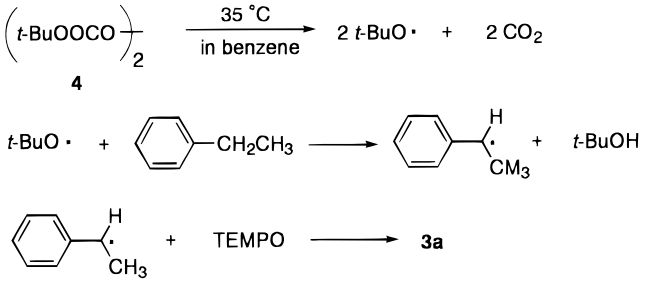
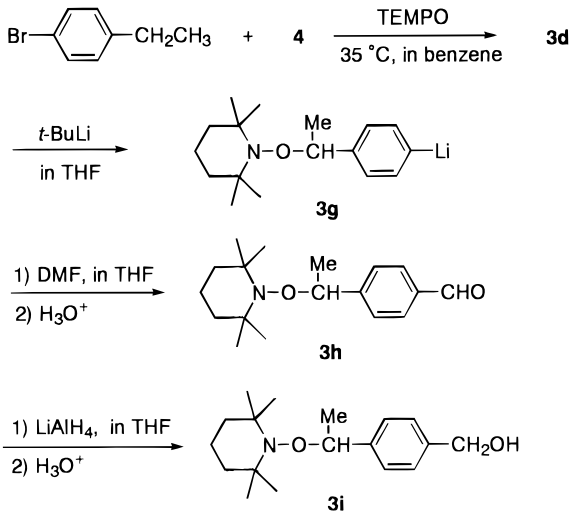
Scheme 1



Scheme 2



Alkoxyamines **3d**, **3e**, and **3f** were prepared in benzene using small mounts of the corresponding ethylbenzenes to avoid wasting the expensive ethylbenzenes. Furthermore, since the ethylbenzenes have high boiling points,[19] it is difficult to remove them at room temperature if they are used as solvent. When the reaction of 4-bromoethylbenzene with **4** was carried out in benzene (10 mL) using 8.0 equiv of the ethylbenzene (16.9 mmol) and 1.6 equiv of **4** (∼3.4 mmol) for TEMPO (2.11 mmol), **3d** was obtained in 88% yield (based on TEMPO) after column chromatographic separation. When 4.0, 2.0, and 1.0 equiv of the ethylbenzene were employed (**4** and TEMPO are constant), the yields were 77, 56, and 36%, respectively. The reaction of 4.0 equiv of 4-(ethoxycarbonyl)ethylbenzene with 1.6 equiv of **4** in the presence of 1.0 equiv of TEMPO gave **3e** in 50% yield, while the reaction of 4.0 equiv of 4-methoxyethylbenzene with 1.6 equiv of **4** in the presence of 1.0 equiv of TEMPO gave **3f** in 91% yield. Accordingly, it can be said that the reaction with ethylbenzenes carrying an electron-donating group gives high yields of alkoxyamines. Crystallization of the alkoxyamines from pentane or methanol gave colorless plates (**3d**, **3e**)[20,21] or needles (**3f**).[22]

Although **3d** was previously prepared by heating a mixture of di-*tert*-butyl peroxide and TEMPO in ethylbenzene at 125 °C, the yield was low (32%), and it was obtained as a colorless oil.[9] No crystallization of the product suggests that it is contaminated with impurities.

Functionalized alkoxyamines **3h** and **3i** were prepared, starting from **3d**. The outline for the preparation is described in Scheme 2. (4-Bromophenyl)alkoxyamine **3d** was converted to lithio compound **3g** in >95% yield on treatment with *t*-BuLi in ether at −78 °C. The high yield of **3g** is in accordance with the observation that

Scheme 3

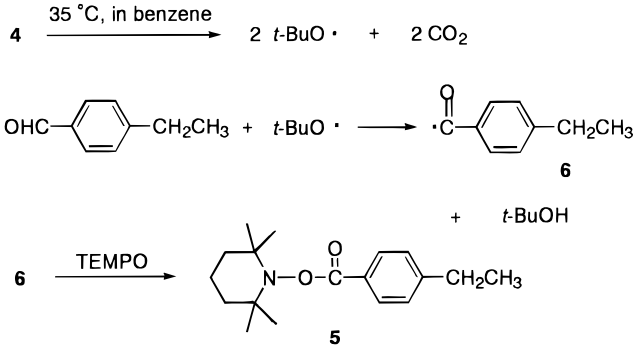


Table 1. Results of Polymerization of Styrene Initiated by 3d-f and 3h at 120 °C[a]

run	alkoxyamine[b]	time (h)	yield[c](%)	M_n[d]	M_w/M_n[d]
1	**3d**	15	53	18 200	1.15
2	**3e**	30	68	23 200	1.17
3	**3f**	30	63	23 500	1.19
4	**3h**	15	51	18 100	1.16
5	**3h**	30	73	25 200	1.15

[a] Styrene 0.909 g (8.73 mmol). [b] The concentration, 20.0 mM. [c] Determined by polymer weights. [d] Determined by GPC (Tosoh 8020 series equipped with TSK-gel columns G5000HHR, GMultiporeHXL-M, and GMHHR-L) using THF as eluant.

the alkoxyamine group is stable to strong bases such as alkyllithiums.[23] Treatment of **3g** with DMF gave the corresponding (4-formylphenyl)alkoxyamine **3h** in 95% yield.[24] Reduction of **3h** with $LiAlH_4$ in THF afforded **3i** in 86% yield as a colorless oil.[25]

As an alternating method for preparation of **3h**, the reaction of 4-formylethylbenzene with **4** in the presence of TEMPO was attempted. Although a mixture of 3.0 equiv of 4-formylethylbenzene, 1.6 equiv of **4**, and 1.0 equiv of TEMPO in benzene was stirred at 35 °C for 3 h under nitrogen, the characteristic red color due to TEMPO did not completely disappear. TLC inspection of the reaction mixture showed two spots. One is due to 4-formylethylbenzene and the other is due to the product. The reaction mixture was concentrated and the residue chromatographed to give **5** in 60% yield.[26]

The structure was elucidated by the ^{1}H NMR and IR spectra. In the ^{1}H NMR spectrum the presence of TEMPO moiety was shown by two singlets at 1.12 and 1.272 ppm due to the four methyl groups at the 2 and 6 positions of the piperidine ring. No disappearance of the triplet at 1.267 ppm and the quintet at 2.72 ppm indicated no reaction of the ethyl group. Furthermore, disappearance of the singlet due to the formyl proton at 10.00 ppm showed that the *tert*-butoxyl radical abstracted preferentially the formyl hydrogen atom from 4-formylethylbenzene to give **6** (see Scheme 3).[27] On the basis of the NMR results the compound was identified to be **5**. This structure was further supported by the IR spectrum, which showed the presence of an ester group by the absorption peaks at 1750 and 1260 cm^{-1}. Consequently, the preparation of **3h** by this route was shown to be impossible.

Bulk polymerization of styrene initiated by alkoxyamines **3d**−**f** and **3h** was carried out at 120 °C. The results are summarized in Table 1. In any case the polydispersity is <1.3, indicating that these functionalized alkoxyamines can be used for the syntheses of controlled macromolecular architectures.

In conclusion, the present method gave alkoxyamines in high yields. Since the procedure is quite simple, this

method will be useful for preparation of alkoxyamines, although extreme care should be taken when handling **4**. Functionalized alkoxyamines **3h** and **3i**, as well as the lithio alkoxyamine **3g**, were prepared from **3d** in high yields. These functionalized alkoxyamines are useful for the syntheses of new controlled macromolecular architectures.

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(14) While the present work was in progress, Priddy et al. reported the synthesis of **3a** by reaction of **4** with ethylbenzene in the presence of TEMPO: Howell, B. A.; Pan, B.; Priddy, D. B. *Polym. Prepr.* **1997**, *76*, 387.
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(16) General procedure for preparation of alkoxyamines **3a**−**c**. A solution of a nitroxide radical (3.14 mmol) and **4** (∼0.77 g, ∼3.3 mmol) (Caution! *do not scrape the crystals*) in ethylbenzene (20 mL) was stirred at 35 °C under a nitrogen atmosphere until the characteristic red color of nitroxide disappeared (ca. 3 h). The reaction mixture was then concentrated to ca. 1 mL by evaporation under reduced pressure at room temperature, and the residue was chromatographed on silica gel using 1:10 ethyl acetate−hexane to give almost pure compounds of **3a**−**c** as a colorless oil. Crystallization of **3a** from pentane or ethanol and subsequent cooling to −20 °C gave colorless needles. **3a**:[8,9] ^{1}H NMR ($CDCl_3$) δ 0.65 (s, Me, 3 H), 1.02 (s, CH_3, 3 H), 1.16 (s, CH_3, 3 H), 1.29 (s, CH_3, 3 H), 1.48 (d, J = 6.8 Hz, CH−C**H**$_3$, 3 H), 1.3−1.6 (br m, $(CH_2)_3$, 6 H), 4.77 (q, J = 6.8 Hz, C**H**CH_3, 1 H), 7.21−7.33 (m, aromatic, 5 H).
(17) **3b**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.64 (s, Me, 3 H), 1.03 (s, Me, 3 H), 1.17 (s, CH_3, 3 H), 1.26 (s, CH_3, 3 H), 1.49 (d, J = 6.8 Hz, CHC**H**$_3$, 3 H), 1.40−1.63 (br m, $(CH_2)_2$, 4 H), 4.66 (q, J = 6.8 Hz, C**H**CH_3, 1 H), 7.22−7.35 (m, aromatic, 5 H).
(18) **3c:**[13] colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, *t*-Bu, 9 H), 1.31 (s, *t*-Bu, 9 H), 1.46 (d, J = 6.8 Hz, CHC**H**$_3$, 3 H), 4.82 (q, J = 6.8 Hz, C**H**CH_3, 1 H), 7.21−7.33 (m, aromatic, 5H).
(19) Boiling points are 204 (4-bromoethylbenzene), 213 (4-(ethoxycarbonyl)ethylbenzene), and 195 °C (4-methoxyethylbenzene).
(20) **3d**:[9] mp 57−59 °C; ^{1}H NMR ($CDCl_3$) δ 0.64 (s, CH_3, 3 H), 1.01 (s, CH_3, 3 H), 1.15 (s, CH_3, 3 H), 1.27 (s, CH_3, 3 H), 1.44 (d, J = 6.8 Hz, CHC**H**$_3$, 3 H), 1.35−1.6 (br m, $(CH_2)_3$, 6 H), 4.73 (q, J = 6.8 Hz, C**H**CH_3, 1 H), 7.19 (d, J = 8.3 Hz, aromatic, 2 H), 7.43 (d, J = 8.3 Hz, aromatic, 2 H). Calcd for $C_{17}H_{26}BrNO$: C, 60.00; H, 7.70; N, 4.12. Found: C, 59.93; H, 7.68; N, 3.82.
(21) **3e**: mp 62−64 °C; IR (KBr) 1715 (C═O) and 1280 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 0.62 (s, CH_3, 3 H), 1.02 (s, CH_3, 3 H), 1.17 (s, CH_3, 3 H), 1.29 (s, CH_3, 3 H), 1.39 (t, J = 6.8 Hz, CH_2C**H**$_3$, 3 H), 1.48 (d, J = 6.8 Hz, CHC**H**$_3$, 3 H), 1.34−1.58 (br m, $(CH_2)_3$, 6 H), 4.37 (q, J = 6.8 Hz, C**H**$_2$$CH_3$, 2 H), 4.82 (q, J = 6.8 Hz, C**H**CH_3, 1 H), 7.38 (d, J = 8.3 Hz, aromatic, 2 H), 7.99 (d, J = 8.3 Hz, aromatic, 2 H). Calcd for $C_{20}H_{31}NO_3$: C, 71.82; H, 9.34; N, 4.19. Found: C, 72.03; H, 9.22; N, 3.87.
(22) **3f**: mp 73−74 °C; ^{1}H NMR ($CDCl_3$) δ 0.65 (s, CH_3, 3 H), 1.01 (s, CH_3, 3 H), 1.15 (s, CH_3, 3 H), 1.28 (s, CH_3, 3 H), 1.2−1.6 (br m, $(CH_2)_3$, 6 H), 1.46 (d, J = 6.8 Hz, CHC**H**$_3$, 3 H), 3.80 (s, OCH_3, 3 H), 4.73 (q, J = 6.8 Hz, C**H**CH_3, 1 H), 6.85 (d, J = 8.8 Hz, aromatic, 2 H), 7.24 (d, J = 8.8 Hz, aromatic, 2 H). Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.32; H, 9.77; N, 4.52.
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(24) **3h**: a stirred solution of 1.55 g (4.6 mmol) of **3d** in 40 mL of dry ether under nitrogen was cooled in a dry ice MeOH bath. After a pentane solution of *t*-BuLi (1.64 M) (4.5 mL, 7.4 mmol) was added with a syringe and the resulting mixture stirred for 1 h at the same temperature, dry DMF (2.0 mL, 26 mmol) was added with a syringe. After the mixture was gradually raised to 0 °C, aqueous NH_4Cl was added at 0 °C and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel using 1:4 hexanes−ethyl acetate to give an almost pure compound of **3h** in 95% yield. crystallization from pentane gave colorless plates: mp 92−93 °C; IR (KBr) 1700 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 0.63 (s, CH_3, 3 H), 1.03 (s, CH_3, 3 H), 1.18 (s, CH_3, 3 H), 1.30 (s, CH_3, 3 H), 1.49 (d, J = 6.8 Hz, CHC**H**$_3$, 3 H), 1.35−1.6 (br m, $(CH_2)_3$, 6 H), 4.85 (q, J = 6.8 Hz, C**H**CH_3, 1 H), 7.48 (d, J = 8.3 Hz, aromatic, 2 H), 7.84 (d, J = 8.3 Hz, aromatic, 2 H), 10.00 (s, CHO, 1 H). Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.59; H, 9.37; N, 4.60.
(25) **3i**: a solution of 304 mg (1.05 mmol) of **3h** in 5 mL of anhydrous THF was added dropwise to a stirred suspension of 63 mg (1.66 mmol) of $LiAlH_4$ in 10 mL of anhydrous THF. After the resulting suspension was stirred for 2 h at room temperature, small amounts of MeOH and then H_2O were added. The mixture was then extracted with CH_2Cl_2, and the extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel with 1:1 ethyl acetate−hexane to give **3i** in 82% yield (0.251 g, 0.86 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.67 (s, CH_3, 3 H), 1.02 (s, CH_3, 3 H), 1.16 (s, CH_3, 3 H), 1.29 (s, CH_3, 3 H), 1.47 (d, J = 6.8 Hz, CHC**H**$_3$, 3 H), 1.35−1.6 (br m, $(CH_2)_3$, 6 H), 4.69 (s, C**H**$_2$OH, 2 H), 4.79 (q, J = 6.8 Hz, C**H**CH_3, 1 H), 7.32 (s, aromatic, 4 H).
(26) Reaction of 4-formylethylbenzene with **4** in the presence of TEMPO: A solution of TEMPO (0.386 g, 2.47 mmol), **4** (∼0.94 g, ∼4.0 mmol), and 4-formylethylbenzene (1.03 g, 7.65 mmol) in benzene (10 mL) was stirred at 35 °C for 3 h under a nitrogen atmosphere. After the reaction mixture was concentrated to ca. 1 mL by evaporation under reduced pressure at room temperature, the residue was chromatographed on silica gel using benzene to give almost pure compounds of **5** in 60% yield as a colorless oil: IR (neat) 1750 (C═O), 1260 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, CH_3, 6 H), 1.267 (t, J = 7.3 Hz, CH_2C**H**$_3$, 3 H), 1.272 (s, CH_3, 6 H), 1.4−1.8 (br m, $(CH_2)_3$, 6 H), 2.72 (q, J = 7.3 Hz, C**H**$_2$$CH_3$, 2 H), 7.29 (d, J = 8.3 Hz, aromatic, 2 H), 8.00 (d, J = 8.3 Hz, aromatic, 2 H).
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