ORGANIC LETTERS

2004
Vol. 6, No. 13
2233−2235

Novel Methodology for the Synthesis of *N*-Alkoxyamines

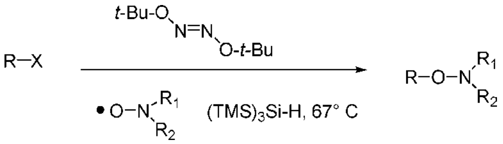
Rebecca Braslau,* Anna Tsimelzon, and Jennifer Gewandter

Department of Chemistry and Biochemistry, University of California−Santa Cruz, Santa Cruz, California 95064

braslau@chemistry.ucsc.edu

Received April 20, 2004

ABSTRACT



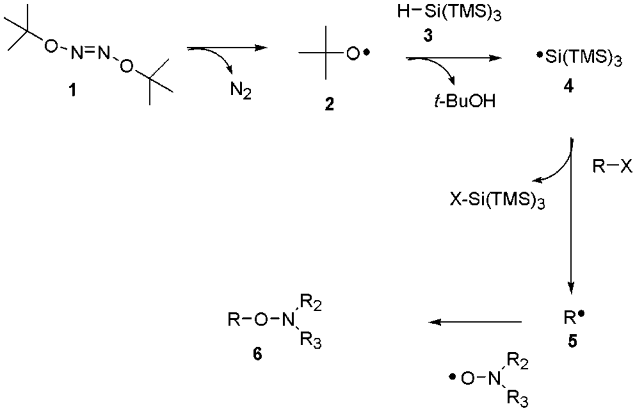
We report a new methodology for the synthesis of the *N*-alkoxyamines, which can be used as initiators in "living" free radical polymerization. Silyl radical abstraction from alkyl halides allows the synthesis of *N*-alkoxyamines inaccessible by other methods.

N-Alkoxyamines are commonly prepared by generating carbon radicals from the corresponding alkyl halides followed by trapping with nitroxides.[1] Tris(trimethyl)silyl radicals readily abstract halogen atoms from alkyl halides.[2] In this methodology, we now demonstrate the use of silyl radicals to generate alkyl radicals from the corresponding alkyl halides in the presence of a nitroxide trap, using a stoichiometric radical initiator.

This new methodology offers a number of potential advantages over other methods. For instance, the use of toxic reagents such as hydrazine[3] or tin hydride[4] is avoided. One can readily prepare *tert*-butyl and *i*-propyl *N*-alkoxyamines, which are not possible by other methods. Furthermore, the method allows synthesis of *N*-alkoxyamines with hydroxyl and carboxyl functionalities. Incorporation of functionality on the *N*-alkoxyamine provides functional handles to allow for pre- or postpolymerization modification, applications including attachment of polymers to surfaces, or end-capping with affinity labels or biomolecules.

The reaction to prepare *N*-alkoxyamines entails use of *tert*-butyl hyponitrite[5] **1** as a thermal radical initiator, tris(trimethyl)silane, an alkyl halide, and a nitroxide. The proposed mechanism for the reaction is outlined in Scheme 1. Upon heating, the oxygen−nitrogen bond in *tert*-butyl hyponitrite **1** undergoes homolytic cleavage generating 2 equiv of *t*-butoxy radical **2**, which in turn abstracts hydrogen from commercially available tris(trimethylsilyl)silane **3**[6] to generate silicon-centered radical **4**. The intermediate silyl radical **4** abstracts halogen from the alkyl halide to generate carbon

Scheme 1



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[1] (a) Braslau, R.; Burill, L. C.; Siano, M.; Naik, N.; Howden, R.; Mahal, L. K. *Macromolecules* **1997**, *30*, 6445. (b) Matyjaszewaki, K.; Woodworth, B. E.; Zhang, X.; Gaynor, S. G.; Metzner Z. *Macromolecules* **1998**, *31*, 5955. (c) Benoit, D.; Chaplinsky, V.; Braslau, R.; Hawker, C. *J. Am. Chem. Soc.* **1999**, *121*, 3904.

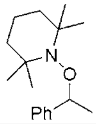
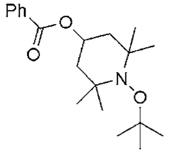
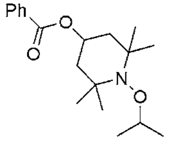
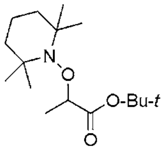
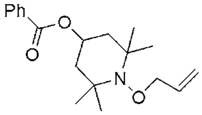
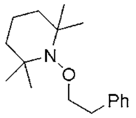
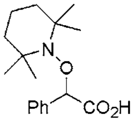
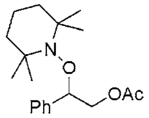
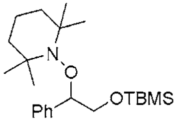
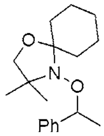
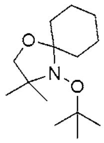
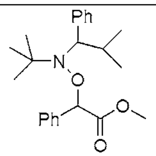
[2] For a review, see: Chatgilialoglu, C.; Ferreri, C.; Gimisis, T. In *The Chemistry of Organic Silicon Compounds*; Rapport, S., Apeloig, Y., Eds.; Wiley: Chichester, 1998; Vol.2, Chapter 25, pp 1539−1579.

[3] Braslau, R.; Burill, L. C.; Siano, M.; Naik, N.; Howden, R.; Mahal, L. K. *Macromolecules* **1997**, *30*, 6445.

[4] (a) Nagashima, T.; Curran, D. P. *Synlett* **1996**, *4*, 331. (b) Marque, S.; Fischer, H.; Baier, E.; Studer, A. *J. Org. Chem.* **2001**, *66*, 1146.

10.1021/ol049271v CCC: $27.50

Table 1. Synthesis of *N*-Alkoxyamines

entry	R-X	product	yield
1 2	Br Cl		48%[b] no rxn.
3	Br		27%[a]
4 5 6	Br I Cl		14%[a] 52%[a] no rxn.
7	Br		42%[a] 49%[b]
8	Br		60%[a]
9 10 11	I Br Cl		53%[a] c no rxn
12	Br		33%[a]
13	I		64%[a]
14	Br		68%[b]
15	Br		26%[a]
16	Br		55%[a]
17	Br		50%[d]

[a] Performed with 1.0 equiv of alkyl halide. [b] Performed with 2.0 equiv of alkyl halide. [c] Ratio of alkyl halide to product was 5:1 as determined by ^{1}H NMR of the crude product. [d] Performed with 2.0 equiv of nitroxide.

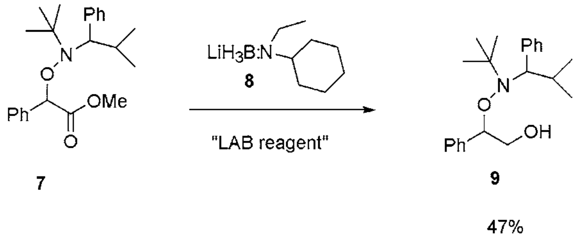
radical **5**, which is then trapped by nitroxide to give *N*-alkoxyamine **6**. Since trapping of the carbon radical by nitroxide terminates the radical sequence, a minimum of 0.5 equiv of *tert*-butyl hyponitrite is required for complete conversion, as overall this is not a radical chain sequence.

The results are summarized in the Table 1. This new methodology allows generation of a variety of carbon radicals such as benzylic, allylic, tertiary, α-carbonyl, secondary, and even primary alkyl radicals, which can be trapped with various nitroxides to generate *N*-alkoxyamines. The reaction is selective for bromides and iodides over chlorides as demonstrated by entries **2**, **6**, and **11**. Better yields were obtained with iodides than bromides.

Of particular interest is entry **17** in Table 1, which gave product **7**. This *N*-alkoxyamine incorporates an ester functionality and is made using the TIPNO nitroxide developed by this lab in conjuction with the Hawker lab at IBM for nitroxide-mediated polymerization.[7] *N*-Alkoxyamine initiators bearing this α-hydrogen nitroxide have been demonstrated to give polymers with good control of both molecular weight and low polydispersity. As compared to the use of TEMPO, use of this less sterically demanding nitroxide in this tris(trimethylsilyl)silane procedure suffers from competitive reduction of the nitroxide to the corresponding amine.[8] Thus, reasonable yields were obtained by using an excess (2.0 equiv) of nitroxide. To provide evidence for nitroxide reduction under the reaction conditions, 1.0 equiv of the TIPNO nitroxide was mixed with 1.0 equiv of *tert*-butyl hyponitrite **1** and 1.0 equiv of tris(trimethylsilyl)silane **3** in benzene at 60 °C for 2 h. The formation of the corresponding amine was supported by observation of a strong peak at 205 *m*/*e* in the mass spectrum of the crude reaction mixture.

Chemoselective reduction of the ester in compound **7** (Scheme 2) using lithium aminoborohydride reagent[9] (LAB) **8** produced compound **9** in 47% yield, which contains an unprotected hydroxyl group. This free alcohol can be used to append a variety of species onto the intiator or to anchor the initiator onto a solid support.

Scheme 2



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(5) For the synthesis of *tert*-butyl-hyponitrite, see: Mendenhall, G. D. *Tetrahedron Lett.* **1983**, *24*, 451.

(6) (a)Chatgilialoglu, C. *Chem. Rev.* **1995**, *95*, 1229. (b) Chatgilialoglu, C.; Newcomb, M. *Adv. Organomet. Chem.* **1999**, *44*, 67.

(7) Benoit, D.; Chaplinsky, V.; Braslau, R.; Hawker, C. J. *J. Am. Chem. Soc.* **1999**, *121*, 3904.

(8) Lucarini, M.; Marchesi, E.; Pedulli, G. F.; Chatgilialoglu, C. *J. Org. Chem.* **1998**, *63*, 1687.

(9) Fisher, G. B.; Fuller J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378.

A typical reaction procedure is illustrated by the formation of the *tert*-butyldimethylsiloxy-protected alcohol shown in entry **14**: 1-bromo-1-phenyl-2-(*tert*-butyldimethylsiloxy)-ethane (241.5 mg, 0.77 mmol) was combined with tris(trimethylsilyl)silane (94.5 mg, 0.38 mmol), *tert*-butyl hyponitrite (66.2 mg, 0.38 mmol), and TEMPO (0.38 mmol, 59.4 mg). The mixture was dissolved in 1.3 mL of benzene, and the solution was heated to 65−70 °C for 2 h under N_2. The benzene was then removed by distillation. The crude material was dissolved in 30 mL of ether and washed three times with 30 mL of water. The organic phase was dried over $MgSO_4$ and filtered. Volatiles were removed in vacuo giving 222 mg of orange oil. Purification by flash chromatography using 49:1 hexane/ethyl acetate gave 102 mg (68% yield) of compound **14** as a colorless oil.

In summary, this methodology provides access to primary, secondary, and tertiary *N*-alkoxyamines from a variety of nitroxides. Both alkyl and functionalized groups can be incorporated, making available modified initiators for nitroxide-mediated polymerization to prepare designed materials for a variety of applications in nanotechnology.

Acknowledgment. This work was supported by the National Science Foundation (CHE-0078852 and CHE-0243786). We would like to thank Professor Bakthan Singaram for helpful discussions on the use of the LAB reagent.

Supporting Information Available: The characterization of compounds in entries 1−17 of Table 1 as well as characterization of compound **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049271V