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A convenient synthesis of functionalized alkoxyamines as initiators for living free radical polymerization

Naoya Sugimoto[1], Atsushi Narumi[1], Toshifumi Satoh[1], Harumi Kaga[2] Toyoji Kakuchi[1](✉)

[1] Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan
[2] National Institute of Advanced Industrial Science and Technology (AIST), 2-17-2-1 Tsukisamu-Higashi, Toyohira, Sapporo 062-8517, Japan
Tel. (Fax): +81-11-706-6602; e-mail: kakuchi@poly-mc.eng.hokudai.ac.jp

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Summary

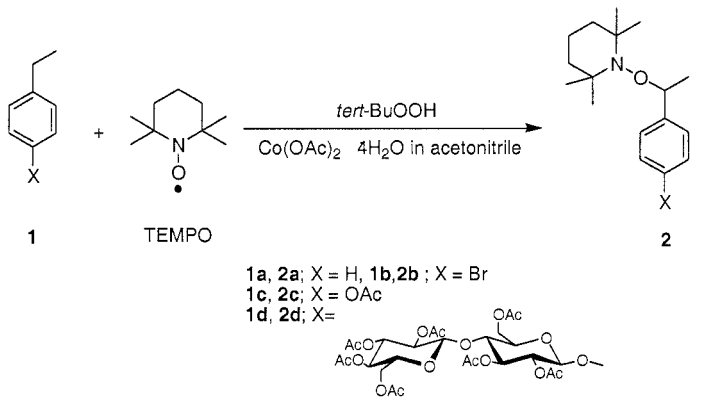
2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) was reacted with ethylbenzene (**1a**), 1-bromo-4-ethylbenzene (**1b**), and 4-ethylphenyl acetate (**1c**), respectively, using *tert*-BuOOH/Co(OAc)·$4H_2O$ in acetonitrile at room temperature. The reactions produced the respective TEMPO-adducts (**2a**, **2b**, and **2c**) in the yields of 37, 44, and 45 %, which were based on TEMPO. Similarly, TEMPO was reacted with 4-ethylphenyl 2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-D-cellobioside (**1d**) to afford the glycoconjugated TEMPO-adduct (**2d**) in 45 % yield, which was based on **1d**. These results indicated that the reaction has the potential to become an easy and also safe strategy, which provided various functionalized alkoxylamines.

Introduction

Various functionalized alkoxyamines have been designed and synthesized as an initiator for the living free radical polymerization leading to well-defined macromolecular architectures, such as block, graft, and star polymers [1]. Since Hawker et al. reported the synthesis of 2,2,6,6-tetramethyl-1-(1-phenylethoxy)-piperidine (**2a**) from the reaction of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and an excess amount of styrene in the presence of benzoyl peroxide [2], a few synthetic methods of alkoxyamines have been reported. They are classified into two types as 1) ethylbenzene derivatives that reacted with the *tert*-butoxyl radical (*tert*-BuO•) and then coupled with the nitroxyl radical [3,4], and 2) styrene derivatives that reacted with the nitroxyl radical in the presence of Jacobsen's catalyst as (salen)Mn(III) [5]. However, these methods involved several drawbacks when used, for example, di-*tert*-butyl diperoxyoxalate is unstable and explosive [6], di-*tert*-butyl peroxide has a relatively low reactivity, and the latter type requires a large amount of an expensive catalyst.

tert-Butyl hydroperoxide (*tert*-BuOOH) is commercially available and easy to handle, because its decomposition temperature is relatively high at ca. 100 °C, resulting in its safe storage at room temperature. In addition, the reaction of *tert*-BuOOH with a

catalytic amount of transition metals, such as cobalt salt, is one of the convenient methods of generating *tert*-BuO• along with *tert*-butylperoxy radical (*tert*-BuOO•) [7]. Thus, of great interest is to apply this method of generating oxy radicals to the synthesis of alkoxyamines. In this study, we report the safe and easy method of synthesizing functionalized alkoxyamines (**2a-e**) from the reaction of ethylbenzene (**1a**) and its *p*-substituted derivatives (**1b-e**) and TEMPO using *tert*-BuOOH/ $Co(OAc)_2 \bullet 4H_2O$, as shown in Scheme 1.



Scheme 1

Experimental

Measurements

The ^1H NMR spectra were recorded using a JEOL JNM-A400II spectrometer (400 MHz) with tetramethylsilane as the internal standard in chloroform-*d*.

Materials

Ethylbenzene and $Co(OAc)_2 \bullet 4H_2O$ were obtained from Kanto Chemical Co., Inc. 4-Bromo ethylbenzene was obtained from Acros Organics. 4-Ethylphenyl acetate was obtained from Tokyo Kasei Kogyo Co., Ltd. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) was obtained from Aldrich. *tert*-BuOOH was obtained from Merck. Acetonitrile was purified by distillation over calcium hydride.

*2,2,6,6-Tetramethyl-1-(1-phenylethoxy) piperidine (**2a**)*

To a solution of TEMPO (0.75 g, 4.7 mmol), $Co(OAc)_2 \bullet 4H_2O$ (27 mg, 0.11 mmol), and ethylbenzene (**1a**) (1.0 g, 9.4 mmol) in acetonitrile (1.5 mL) was added *tert*-BuOOH (0.94 mL, 9.4 mmol) under a nitrogen atmosphere. The color of the reaction solution changed from orange to dark green. After stirring for 16 h at room temperature, the reaction mixture was filtered off and the filtrate was concentrated under reduced pressure at room temperature. The residue was diluted with dichloromethane and then washed with water. After the organic layer was dried with anhydrous sodium sulfate and evaporated to dryness, the crude product was purified

by flash chromatography on silica gel with dichloromethane to obtain **2a** as a white solid. M.p., 45.5-47 °C (lit. [2], 46-47 °C). Yield, 0.46 g (37 % based on TEMPO).

*4-[1-(2,2,6,6-Tetramethylpiperidinyloxyl)ethyl]phenyl 2,3,6,2',3',4',6'-hepta-O-acetyl-β-D-cellobioside (**2d**)*

The above procedure was applied for the reaction of TEMPO (0.20 g, 1.30 mmol), $Co(OAc)_2•4H_2O$ (27 mg, 0.11 mmol), 4-ethylphenyl 2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-D-cellobioside (**1d**) (0.80 g, 1.1 mmol) [8], and *tert*-BuOOH (0.32 mL, 3.24 mmol) in acetonitrile (2.5 mL). After purification by flash chromatography on silica gel, **2d** was obtained as a white solid. Yield, 0.44 g (45 % based on **1d**)

Results and Discussion

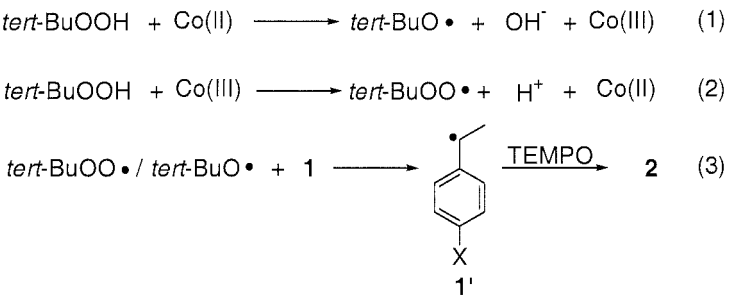
The reaction of the ethylbenzene derivatives (**1**) and TEMPO with *tert*-BuOOH/$Co(OAc)_2•4H_2O$ was carried out in acetonitrile at room temperature under nitrogen. The reaction proceeded heterogeneously, because $Co(OAc)_2•4H_2O$ was insoluble in acetonitrile. The color of the reaction system changed from red to dark green, indicating that Co(II) was oxidized with *tert*-BuOOH into Co(III) [9]. After 16 h, the reaction solution was diluted with dichloromethane, the catalyst was removed by filtration, the solvent was evaporated, and the residue was purified by chromatography on silica gel. Table 1 is summarized the synthetic results. Ethylbenzene (**1a**), 1-bromo-4-ethylbenzene (**1b**), and 4-ethylphenyl acetate (**1c**) are commercially available inexpensive reagents, so that excess amounts of them versus TEMPO were used. For runs 1, 2, and, 3, the reactions were carried out with the molar ratio of [**1**]/[TEMPO]/[[*tert*-BuOOH]/[$Co(OAc)_2•4H_2O$] = 1/0.5/1/0.025. The yield based on TEMPO was 37 % for **2a**, 44 % for **2b**, and 45 % for **2c**. In addition, the synthetic method was useful for a complicated and specially designed ethylbenzene, 4-ethylphenyl 2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-D-cellobioside (**1d**), which was applicable as the initiator for preparing the well-defined end-cellobiosyl polystyrene [10]. Thus, it is desirable that **1d** should be converted into **2d** as much as possible. For run 4, an excess amount of TEMPO towards **1d** was employed as [TEMPO]/[**1d**] = 1.2. The glycocojugated TEMPO, **2d**, was obtained in a 45 % yield based on **1d**.

Table 1. Synthesis of 2,2,6,6-tetramethyl-1-(1-phenylethoxy)-piperidine derivatives (**2a-d**) by the reaction of ethylbenzenes (**1a-d**) and TEMPO with *tert*-BuOOH in the presence of $Co(OAc)_2•4H_2O$ [a]

run no.	**1**	[TEMPO]/[**1**]	[*tert*-BuOOH]/[**1**]	[$Co(OAc)_2•4H_2O$]/[**1**]	Yield, %
1	**1a**	0.5	1.0	0.025	37 [b]
2	**1b**	0.5	1.0	0.025	44 [b]
3	**1c**	0.5	1.0	0.025	45 [b]
4	**1d**	1.2	3.0	0.10	45 [c]

[a] solvent, CH_3CN; temp., room temperature; reaction time, 16 h; [b] based on TEMPO, [c] based on **1d**

The decomposition of *tert*-BuOOH gently occurred in the presence of transition metals at room temperature, and acted as a significant radical source. The catalytic decomposition of *tert*-BuOOH with a cobalt salt has been widely investigated in terms of the autooxidation mechanism [7]. *tert*-BuOOH was decomposed through the Haber–Weiss cycle, producing *tert*-BuO• and *tert*-BuOO•, as shown in eqs. 1 and 2. In addition, *tert*-BuO• and *tert*-BuOO• abstracted the α-hydrogen of **1** to yield the corresponding benzyl radical intermediates (**1'**), and then was trapped with TEMPO to afford **2** (eq. 3). The new strategy based on the catalytic decomposition of *tert*-BuOOH is useful for the synthesis of various alkoxylamines.



Conclusion

We demonstrated that the TEMPO adducts with various functional groups were easily prepared by the reaction of ethylbenzene derivatives and TEMPO using *tert*-BuOOH/$Co(OAc)_2$•$4H_2O$. The advantage of this procedure is that it is easy and safe to operate, and thus we synthesized and used TEMPO adducts having sugar units for the synthesis of new macromolecular structures [10].

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