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A facile amino-functionalization of poly(2-oxazoline)s' distal end through sequential azido end-capping and Staudinger reactions

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ABSTRACT

Facile and quantitative method to introduce primary-amino group into the distal chain end of poly(2-substituted 2-oxazoline)s (POx)s, which have attracted progressive interest as platform polymers for various bio-functionality materials, was established here via two-step reactions; First, termination of cationic polymerization of 2-oxazoline using sodium azide as the end-capping reagent, followed by the conversion of the azido group to an amino group using triphenylphosphine (TPP) by the Staudinger reaction. The azido introduction step and the subsequent amino conversion step was accomplished within 1 h and 3 h, respectively, to ultimately obtain ω-amino-poly(2-ethyl-2-oxazoline) (PEtOx-NH_2) with 96% functionality. The synthesized PEtOx-NH_2 was subjected to ring-opening polymerization of N^{ε}-trifluoroacetyl-L-lysine *N*-carboxy anhydride (Lys(TFA)-NCA) to successfully obtain the block copolymer PEtOx-*b*-PLys(TFA), which can be utilized as a platform polymer to develop polymer therapeutics, thus, demonstrating the versatility of the presently reported procedure for further functionalization of POx derivatives.

1. Introduction

Poly(2-substituted 2-oxazoline) (POx) obtained by living cationic ring-opening polymerization of the corresponding oxazoline monomer, has recently attracted significant attention as a class of functionality polymers, particularly for biomedical applications [1–3]. The substituent on the 2-position of the oxazoline unit gives POxs a variety of functionalities.

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For example, poly(2-methyl 2-oxazoline) (PMeOx) and poly(2-ethyl-2-oxazoline) (PEtOx) are the hydrophilic and biocompatible polymers approved by the U.S. Food and Drug Administration [3,4]. In addition to this, POxs with substituents such as *n*-propyl (PnPrOx) and isopropyl (PiPrOx) have thermo-responsive properties, so that they can exhibit lower critical solution temperature (LCST) in the range of physiological condition [1–3,5,6]. It is also feasible to integrate additional functionalities to POxs by introducing various functional groups, such as amino group [7], alkenyl and alkynyl groups [8], thiol group [9], sugars [10], and so forth, to the side chain of POxs by preparing appropriate monomers with these functional groups or their precursors. The living nature of oxazoline polymerization is also an appealing point. POxs with quite a narrow molecular weight distribution, M_w/M_n as small as 1.01 measured by MALDI-TOF MS, can easily be obtained under optimized conditions [6]. These unique features promote the use of POxs in various biomedical applications, such as surface coating [11,12], bioconjugation [13–15], hydrogels [16,17], and drug/gene carriers [4,18,19].

One of the key issues to further expand the utilities of POxs in the afore-mentioned applications is the development of a facile and quantitative procedure to introduce reactive groups selectively at their chain end for conjugation, tethering, and polymerization chemistry. Particularly, introduction of a primary amino group is attractive considering its wide reactivity. It should be noted that primary amine can initiate polymerization of *N*-carboxyl anhydride (NCA) to produce POx-*b*-poly(amino acid) block copolymers, which may be feasible alternatives to poly(ethylene glycol) (PEG)-*b*-poly(amino acid) block copolymers widely utilized in drug delivery formulations [20,21]. A few procedures have been reported to introduce a primary amino group at the end of POxs. Park et al. and Tauhardt, et al. reported a procedure to introduce phthalimide, followed by conversion to an amino group [22,23]. Meyer *et al.* demonstrated a procedure to introduce 4-(*N*-Boc-amino)-piperidine, followed by deprotection of the Boc group to obtain POx-piperidine-NH_2 [24]. Despite these procedures being able to introduce a primary amino group at the ω-chain end of POxs, it takes a prolonged time period for the reaction to complete.

Here, we have developed a facile and quantitative procedure to introduce a primary amino group into the ω-chain end of POxs: Terminating the living cationic polymerization of oxazolines by the end-capping with sodium azide to obtain azido-terminated POx as the first step [25,26], followed by the Staudinger reaction using Triphenylphosphine (TPP) to convert the azido group to a primary amino group [27,28]. This procedure was completed within several hours, and a high conversion of 96% functionality was obtained. Furthermore, to demonstrate the utility of amino-functionalized POxs for further applications, we conducted a ring-opening polymerization of L-lysine(TFA)-NCA from the synthesized ω-amino-poly(2-ethyl-2-oxazoline) (PEtOx-NH_2) to obtain PEtOx-*b*-poly(L-lysine(TFA)) with a narrow molecular weight distribution, which is expected to be useful as a platform polymer for drug and gene delivery applications.

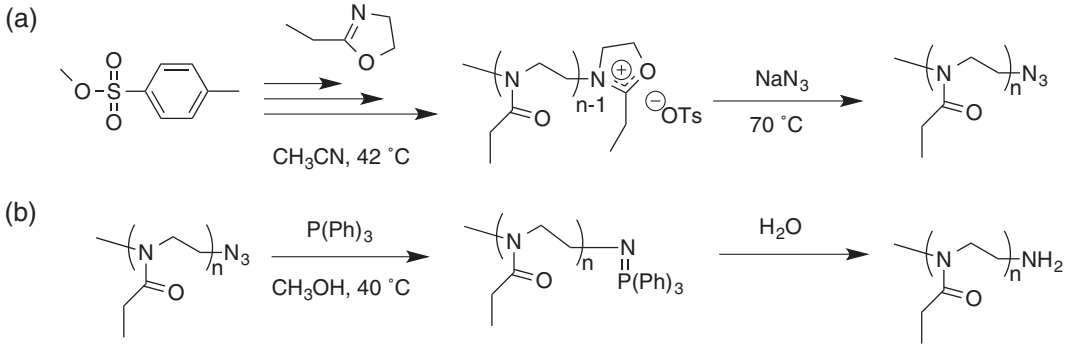
2. Materials and methods

2.1. Materials

2-Ethyl-2-oxazoline (EtOx) (Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan), 2-*n*-propyl-2-oxazoline (nPrOx) (Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan), acetonitrile (Wako Pure Chemical Industry, Osaka, Japan), and dimethyl sulfoxide (DMSO) (Wako Pure Chemical Industry, Osaka, Japan) were used after distillation over calcium hydride. Methyl *p*-toluenesulfonate (Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan) was used after distillation over phosphorus pentoxide. Sodium azide (Wako Pure Chemical industry, Osaka, Japan), triphenylphosphine (TPP) (Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan), and other reagents were used as received. N^{ε}-trifluoroacetyl-L-lysine *N*-carboxy anhydride (Lys(TFA)-NCA) was prepared by the Fuchs-Farthing method [29].

2.2. Synthesis of azido-terminated PEtOx

Synthesis of azido-terminated PEtOx (PEtOx-N_3) is outlined in Scheme 1a. The polymerization of EtOx was carried out according to the literature methods [6,19,22]. Briefly, an initiator of methyl *p*-toluenesulfonate (62 mg, 0.66 mmol) was



Scheme 1. Synthetic route to obtain PEtOx-NH_2. (a) Polymerization of EtOx followed by a termination reaction with NaN_3. (b) Conversion of the azido group to the amino group by one-pot sequential reactions with TPP (Staudinger reaction) and water.

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