

# Facile Procedure for Generating Side Chain Functionalized Poly( $\alpha$ -hydroxy acid) Copolymers from Aldehydes via a Versatile Passerini-Type Condensation

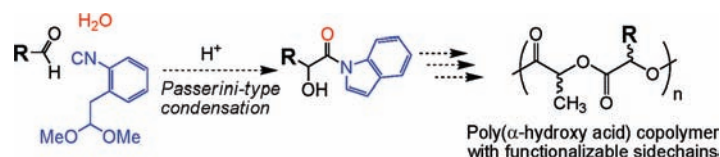
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## ABSTRACT



A general method for synthesizing  $\alpha$ -hydroxy *N*-acylindoles in one-pot via an acid-catalyzed condensation of a convertible isonitrile with water and various aldehydes is presented. These intermediates were incorporated into poly( $\alpha$ -hydroxy acid) copolymers bearing residues with functionalizable side chains, which could be further modified through Cu(I)-catalyzed azide–alkyne cycloaddition reactions. This versatile synthetic strategy provides access to side chain functionalized poly( $\alpha$ -hydroxy acid) copolymers from readily available aldehydes, making it potentially useful as an approach to synthesize biodegradable polymers with new, tunable properties.

Poly(lactic acid) (PLA), the most well-known member of the poly( $\alpha$ -hydroxy acid) class of polymers, has attracted significant interest as biodegradable and biocompatible materials for use in medical applications ranging from surgical sutures<sup>1</sup> to drug delivery devices,<sup>2</sup> as well as for use in commercial goods.<sup>3</sup> As an aliphatic polyester, PLA has inherent limitations due to its insolubility in aqueous media and lack of functionalizable side chains. Simple, general, and scalable methods to incorporate functionality in PLA-based polymers may enable new applications of these materials for other biomedical and commercial uses.<sup>4</sup> Although previous reports describe the preparation of PLA-

based copolymers containing functionalized side chains,<sup>5,6</sup> these methodologies are often laborious or require specialized reagents to obtain a specific, desired functional group in the polymer. Herein, we introduce a strategy for the efficient and versatile synthesis of PLA-based polymers containing side chains with a variety of chemical properties.

PLA is typically prepared industrially by heating D,L-lactide in the presence of a catalyst and an initiator.<sup>3</sup> The few successful attempts to incorporate functional groups into PLA-based copolymers employ copolymerizing D,L-lactide with either functionalized morpholine-2,5-diones<sup>7</sup> or with lactides generated from side chain functionalized  $\alpha$ -hydroxy

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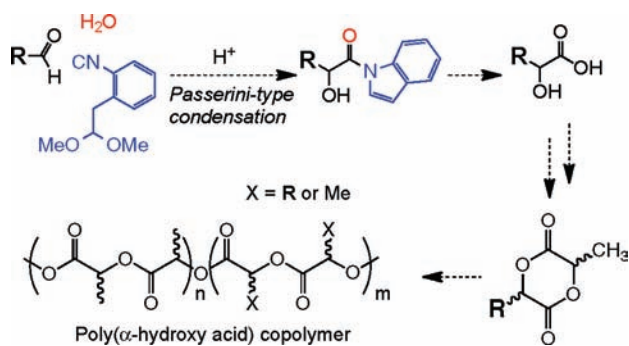
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acids.<sup>6,8</sup> Simple and general access to tailored  $\alpha$ -hydroxy acids and to the subsequent functionalized cyclic copolymerization reagents, however, remains a synthetic challenge. To address this problem, we developed a procedure to gain rapid access to  $\alpha$ -hydroxy acid derivatives using a one-pot, Passerini-type condensation reaction.

The Passerini<sup>9</sup> and Ugi<sup>10</sup> reactions are multicomponent condensations that employ isocyanides to generate carboxamides and bis-amides, respectively. Recently, Kobayashi and co-workers reported<sup>11</sup> that a convertible isocyanide<sup>12</sup> (**1**) can be successfully used in Passerini and Ugi condensations to convert the typically stable carboxamide products to readily cleavable *N*-acylindole intermediates. We, therefore, explored the possibility of using this convertible isocyanide in a Passerini-type condensation reaction to develop a general method for generating  $\alpha$ -hydroxy *N*-acylindoles containing a variety of side chain functionality (Scheme 1). We

**Scheme 1.** Proposed General Condensation of Aldehydes with a Convertible Isonitrile<sup>a</sup>



<sup>a</sup> The resulting *N*-acylindoles may be further converted to side chain functionalized hemilactides and incorporated into poly( $\alpha$ -hydroxy acid) copolymers.

hypothesized that these functionalized  $\alpha$ -hydroxy *N*-acylindoles could be readily hydrolyzed to the corresponding acids and further converted to hemilactides for subsequent incorporation into PLA-based copolymers. A significant advantage of this synthetic approach is its versatility, since this common strategy can potentially generate a large and diverse set of tailored polymers from simple, commercial or readily prepared aldehydes.

We demonstrated that reaction of isocyanide (**1**), acetaldehyde, and water afforded the *N*-acylindole of lactic acid (**2a**) in good yield (Table 1). In this procedure, the putative amide produced from this Passerini-type condensation reaction was

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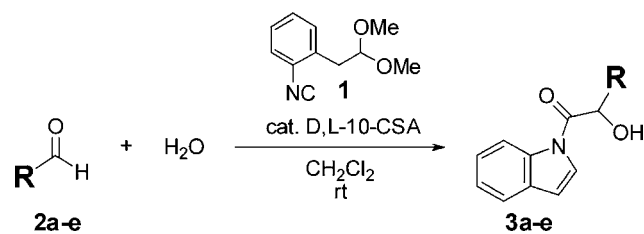
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**Table 1.** Isolated Yields of *N*-Acylindoles from the Passerini-Type Condensation Reaction<sup>a</sup>



entry	compound	aldehyde	yield (%)
1	<b>3a</b>		74
2	<b>3b</b>		67
3	<b>3c</b>		69
4	<b>3d</b>		65
5	<b>3e</b>		69

<sup>a</sup> CSA = camphorsulfonic acid.

transformed *in situ* to an *N*-acylindole in the presence of a catalytic amount of camphorsulfonic acid (CSA), presumably in a similar manner as described previously.<sup>12</sup> To investigate the general utility of these condensation conditions, we tested several aldehydes for the ability to generate side chain functionalized *N*-acylindoles (Table 1). The results indicate that we can introduce a range of chemical properties in good yield using this method; that is, functionality with azide-reactive (**2b**), alkyne-reactive (**2c** and **2d**), hydrophilic (**2d**), or sterically bulky (**2e**) properties. We chose to incorporate side chains from aldehydes **2b–2e** in the condensation reaction in order to provide chemical handles for postpolymerization modification or to introduce other potentially useful chemical or physical properties into the polymer. Functional groups provided by aldehydes **2b–d**, for instance, would lead to PLA-based copolymers that could be modified by utilizing a Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC)<sup>13</sup> reaction. Compound **2d**, in addition to providing a handle for CuAAC, may also impart a degree of water solubility to a polymer that is otherwise insoluble in aqueous solution.<sup>14</sup> Aldehyde **2e** may also afford access to a PLA-based copolymer containing side chains with amine handles upon deprotection of the phthalimide group.<sup>15</sup> To illustrate another potential advantage of this Passerini-type condensation for generating large scale quantities of *N*-acylin-

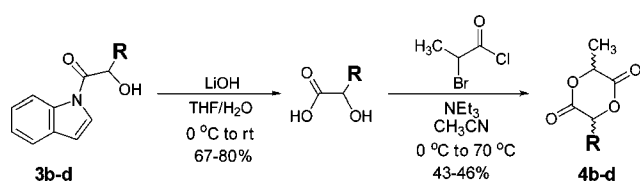
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doles, we prepared multiple grams of **3b** from 4-pentynal in a single condensation reaction.

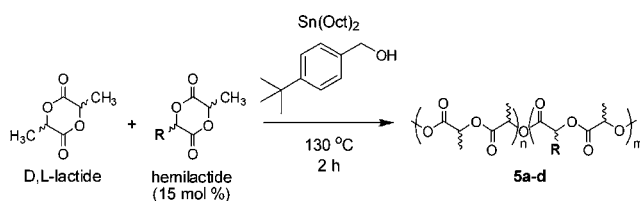
To demonstrate the utility of *N*-acylindoles as functionalized polymeric precursors, we converted compounds **2b–d** to the corresponding hemilactides **4b–d**. The *N*-acylindoles were readily hydrolyzed using LiOH in THF/H<sub>2</sub>O to give the corresponding  $\alpha$ -hydroxy acids in 67–80% isolated yields; these  $\alpha$ -hydroxy acids required minimal purification and were isolated as pure products after solution phase extraction (see Supporting Information for details). Subsequent reaction of  $\alpha$ -hydroxy acids with 2-bromopropionyl chloride afforded hemilactides **4b–d** in moderate yield as mixtures of stereoisomers (Scheme 2).<sup>16</sup>

**Scheme 2.** Scheme for the Facile Two-Step Conversion of  $\alpha$ -Hydroxy *N*-Acylindoles to the Corresponding Hemilactides



To demonstrate these novel hemilactides **4b–d** could be incorporated into PLA-based copolymers, we reacted 15 mol % of **4b–d** with commercial D,L-lactide and catalytic amounts of stannous octoate (as a polymerization catalyst) and 4-*tert*-butylbenzyl alcohol (as an initiator) at 130 °C

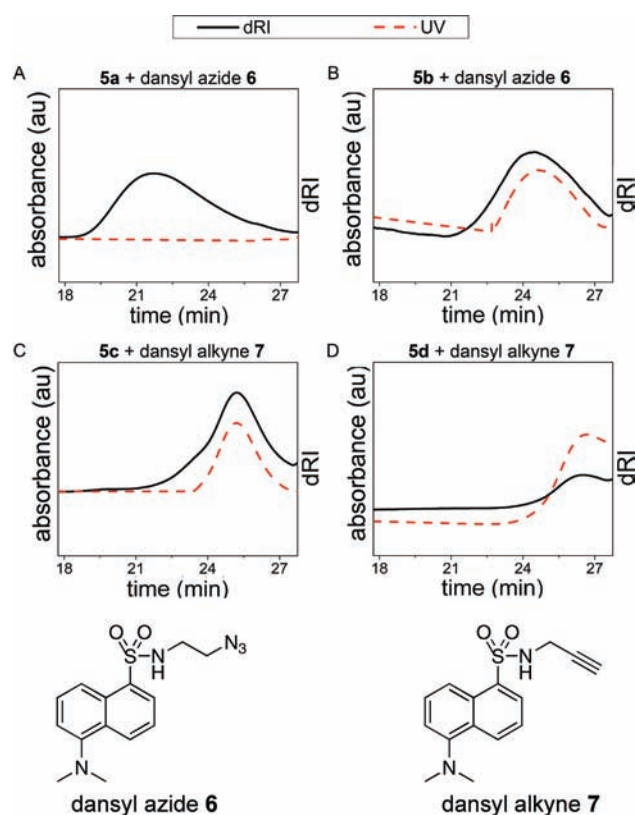
**Table 2.** Incorporation of Functionalized Hemilactides into PLA-based Copolymers



hemilactide	conversion (%) <sup>a</sup>	$10^3 \cdot M_n^b$ (g/mol)	PDI <sup>b</sup> ( $M_w/M_n$ )
none	91	27.4	1.19
	94	22.6	1.11
	76	34.5	1.12
	72	23.1	1.17

<sup>a</sup> Estimated using <sup>1</sup>H NMR. <sup>b</sup> Estimated using Rayleigh ratio values and dRI values obtained by size-exclusion chromatography.

under an inert atmosphere for 2 h. We analyzed the resulting polymers **5b–d** by NMR and gel permeation chromatography (GPC) to estimate the percent conversion of lactide or hemilactide to polymer, the number-average molecular weight ( $M_n$ ), and the polydispersity (PDIs) of the copolymers. As a control, we compared these parameters of copolymers **5b–d** to pure PLA polymer **5a** that was synthesized under the same polymerization conditions. Lactide and hemilactide were efficiently converted to copolymer under these reaction conditions (Table 2). GPC analysis of **5b–d** indicated that these polymerization conditions resulted in polymers with a molecular weight range of 22–32 kDa and PDIs in the range of 1.1–1.2,<sup>17</sup> which were similar in size and dispersity as pure PLA polymer **5a** that was synthesized in the absence of a hemilactide as a dopant. To verify that copolymers **5b–d** were amenable to postpolymerization modification, we subjected **5a–d** to CuAAC conditions<sup>13</sup> in the presence of an excess of a dansyl derivative containing either an azide (**6**) or a terminal alkyne (**7**) group. The UV-active dansyl group incorporated into all three copolymers **5b–d** under these reaction conditions (Figure 1), whereas pure PLA



**Figure 1.** Modification of copolymers **5b–d** using CuAAC click reactions. (A–D) Size exclusion chromatographic traces of crude samples containing CuSO<sub>4</sub> and sodium ascorbate with (A) PLA **5a** and dansyl azide **6**, (B) alkyne-functionalized polymer **5b** and dansyl azide **6**, (C) azide-functionalized polymer **5c** and dansyl alkyne **7**, or (D) azide-functionalized polymer **5d** and dansyl alkyne **7**. The chromatograms of crude polymer-containing solutions were monitored by differential refractive index (dRI, black) and UV absorbance (red). The UV was monitored at  $\lambda = 365$  nm to indicate species containing a dansyl group.

polymer **5a** remained unmodified. These results strongly support that hemilactides **4b–d** were indeed incorporated into polymers **5b–d** and that the functionalized side chains retained their specific reactive properties.

In summary, this work presents an efficient and versatile Passerini-type condensation reaction to generate  $\alpha$ -hydroxy acid derivatives that can be readily incorporated into side chain functionalized PLA-based copolymers. A particularly attractive feature of this method is the capability of incorporating a range of tailored side chain functionality into the polymers from a variety of commercially available or readily prepared aldehydes. Furthermore, the procedure outlined in this work affords access to copolymers at potentially practical scales and makes it possible to incorporate functionality for further modification of the polymer. This new methodology,

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(17) Crude analysis of **5c** and **5d** by size exclusion chromatography revealed at least two populations of polymers. Table 2 reports the characterization of the main polymeric species. For **5c**, a second, smaller polymeric species had a  $M_n$  of  $38.8 \times 10^4$  g/mol and a PDI of 1.27. For **5d**, a second polymeric species had a  $M_n$  of  $7.38 \times 10^3$  g/mol and a PDI of 1.23.

therefore, represents a significant step toward accessing biodegradable and biocompatible materials with improved functional and potentially tunable properties that may find utility in a variety of applications.<sup>5</sup>

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**Supporting Information Available:** Additional experimental details and characterization of molecules. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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