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One-Pot Asymmetric Synthesis of β-Cyanohydroxymethyl α-Amino Acid Derivatives: Formation of Three Contiguous Stereogenic Centers

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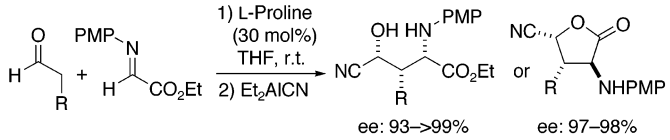
ABSTRACT



One-pot asymmetric Mannich–hydrocyanation reactions are described. Reaction of unmodified aldehydes with *N*-PMP-protected α-imino ethyl glyoxylate in the presence of catalytic amounts of L-proline followed by the addition of Et_2AlCN provided highly enantiomerically pure β-cyanohydroxymethyl α-amino acid derivatives possessing three contiguous stereogenic centers as single diastereomers (93–99% ee). Control of reaction temperature during the cyanation step directed whether cyclization of the products to lactones occurred.

Enantiomerically pure functionalized amino acid derivatives are an extremely important class of compounds because they are potentially bioactive themselves, are components of bioactive peptides, and are synthons for natural products and pharmaceuticals.[1] The development of methodologies for accessing amino acid derivatives has therefore received much attention.[1−3] Here we report an efficient approach to highly enantiomerically pure functionalized amino acid derivatives possessing three contiguous stereogenic centers via one-pot Mannich−hydrocyanation reactions.

Recently we developed direct catalytic enantioselective Mannich-type reactions of unmodified aldehydes with *N*-PMP-protected α-imino ethyl glyoxylate to form aldehyde-

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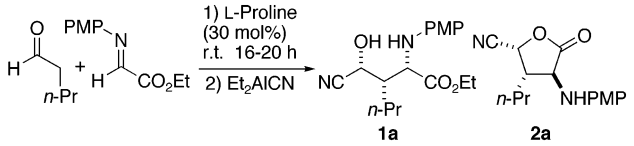
substituted α-amino acid derivatives using catalytic amounts of L-proline.[3a] Because of the aldehyde functionality present in the product, the excellent diastereo- and enantioselectivities of the reaction, and the mild reaction conditions provided by L-proline catalysis,[4] the products should be useful for the further transformations such as nucleophilic reactions on the aldehyde carbonyl to form another carbon−carbon bond without workup/purification. Here we examine the potential of this reaction for further one-pot transformations. We chose a cyanation reaction with Et_2AlCN[5] for the second step in the one-pot sequence. Proline-catalyzed Mannich-type reactions followed by cyanation of the first product aldehyde would provide β-cyanohydroxymethyl α-amino acid derivatives. Cyanohydrins are versatile functional groups in organic synthesis[6] and can be easily transformed to α-hydroxy acid derivatives,[7] α-hydroxy aldehydes,[8] β-hydroxy amines,[9] and amino acid derivatives.[10] Therefore, the one-pot Mannich−cyanation reaction products could be transformed into a wide variety of amino acid derivatives. To the best of our knowledge, our strategy is the first to provide access to chiral amino acid derivatives bearing a cyanohydroxymethyl group at the β position.

First, we examined reaction conditions for the cyanation step in this one-pot sequence (Table 1). When the Mannich-type reaction was performed using valeraldehyde in THF at room temperature according to our procedure[3a] and the reaction mixture was cooled to −78 °C followed by the addition of Et_2AlCN, β-cyanohydroxymethyl α-amino acid derivative **1a** was obtained as a single diastereomer with good yield and high enantioselectivity (61% for two steps, 93% ee) (entry 1) after purification. To complete the reaction, 4 equiv or more of Et_2AlCN was required. Increasing the temperature (−78 °C to rt) of the cyanation step afforded lactone **2a** (60%, 97% ee) (entry 2) with no trace of **1a**. The cyanation at −40 °C also afforded **1a** (40%) as the main product (entry 3) with **2a** (<5%). When dioxane was used as solvent, the reaction also provided **2a** as the main product at rt (entry 4) and a mixture of **1a** and **2a** at 0 °C (data not shown). The formation of either **1a** or **2a** was dependent on the temperature of the cyanation step and was controlled by changing the temperature.

To broaden the scope of this methodology, we demonstrated it efficacy in reactions using a variety of aldehydes (Tables 2 and 3). The reactions involving cyanation at −78 °C afforded cyanohydrin **1** (Table 2) and at increased temperature afforded lactone **2** (Table 3). The yield of either **1** or **2** ranged between 40% and 68%. Excellent enantioselectivities were observed in the case of aldehydes with a longer chain length (R ≥ *n*-pentyl) for the formation of **1**. High enantioselectivities were also observed in the formation of lactone **2**. A single diastereomer was isolated in all cases,

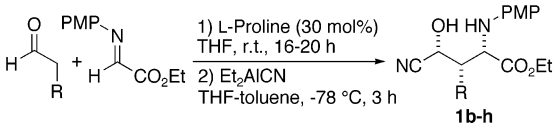
Table 1. Reaction Conditions Effect One-Pot Mannich−Cyanation Reactions To Provide Either **1a** or **2a**[a]

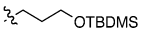


entry	solvent	temp[b]	time[b]	product	yield[c] (%)	ee[d] (%)
1	THF	−78 °C	3 h	**1a**	61	93
2	THF	−78 °C to rt	5 h	**2a**	60	97
3	THF	−40 °C	3 h	**1a**	40	*e*
4	dioxane	rt	18 h	**2a**	40	*e*

[a] PMP = *p*-methoxyphenyl. A mixture of of *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol), valeraldehyde (1.0 mmol), and L-proline (0.15 mmol) in THF or dioxane (5 mL) as indicated was stirred at room temperature for 16−20 h, and Et_2AlCN (1 M in toluene, 2 mmol) was added into the reaction mixture at the temperature shown in this table. [b] Conditions for the cyanation step. [c] Isolated yield after column chomatography. [d] Enantioselectivities were determined by chiral-phase HPLC analysis. [e] Not determined.

Table 2. One-Pot Mannich−Cyanation Reactions to Form **1**[a]



entry	R	product	yield[b] (%)	ee[c] (%)
1[d]	*i*-Pr	**1b**	40	94
2	*n*-Bu	**1c**	60	93
3	*n*-Pent	**1d**	68	98
4	*n*-Hex	**1e**	65	98
5	$PhCH_2$	**1f**	62	>99
6		**1g**	42	>99
7[d]		**1h**	40	>99

[a] A mixture of of *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol), aldehyde (1.0 mmol), and L-proline (0.15 mmol) in THF (5 mL) was stirred at room temperature for 16−20 h, and the reaction mixture was cooled to −78 °C followed by the addition of Et_2AlCN (1 M in toluene, 2.0 mmol except as noted). The mixture was stirred at the same temperature for 3 h. Typical workup with saturated $NaHCO_3$, extraction with ethyl acetate, and silica gel column purification afforded **1**. [b] Isolated yield after column chromatography. [c] Enantioselectivities were determined by chiral-phase HPLC analysis. [d] Et_2AlCN (3.0 mmol) was used.

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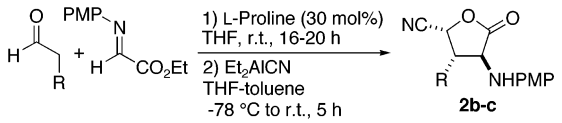
Table 3. One-Pot Mannich−Cyanation Reactions to Form **2**[a]



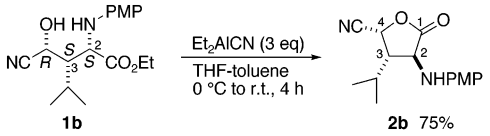
entry	R	product	yield[b] (%)	ee[c] (%)
1[d]	*i*-Pr	**2b**	42	97
2	*n*-Bu	**2c**	62	98

[a] The reaction was performed as described in the footnote in Table 2 except for the temperature for the cyanation step (−78 °C to rt for 5 h). [b−d] See footnotes in Table 2.

in the formation of either **1** or **2**. The presence of other diastereomers was not observed in the ^{1}H NMR after silica gel column purification.[11,12]

The stereochemistries of **1b** and **2b** were determined by NMR study on **2b** and by the transformation of **1b** to **2b**. ROESY analysis of **2b** demonstrated an NOE between the vicinal protons at C3 and C4, and no NOE between the protons at C2 and C3.[12] An NOE was also observed between the methine proton of the isopropyl group and the proton at C2. Therefore, it was confirmed that **2b** has a *trans* relationship between the amino group at C2 and the isopropyl at C3 and a *cis* relationship between the isopropyl and the cyano group at C4 in the γ-lactone. Since **1b** was transformed to **2b** (75%) as a single diastereomer with Et_2AlCN,[13] the relationship between the substituents at the three contiguous stereogenic centers of **1b** was determined to be all *syn* as indicated (Scheme 1). The first step of the one-pot, Mannich-

Scheme 1. Transformation of **1b** to **2b**



type reaction of isovaleraldehyde provided isomer **3** (R = *i*-Pr) that possessed a (*S*) configuration at C2.[3a] Thus the absolute stereochemistry of **2b** was determined to be (2*S*,3*S*,4*R*) and that of **1b** is as indicated.[14] The cyanation product retains the (3*S*) configuration of the major isomer of **3** set at the Mannich-type reaction step.[3a] Cyanohydrin **1b** was obtained from **3** (R = *i*-Pr) without epimerization at C3. This is an advantage of this one-pot sequence because workup/purification of the aldehyde-Mannich products decreases the diastereomeric ratio by epimerization at C3.[3a] The selectivity of cyanation with Et_2AlCN can be explained by a nonchelated transition state model, the Felkin−Anh model[15,16] (Figure 1).

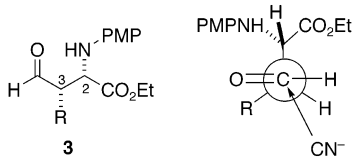


Figure 1. The Mannich-type reaction product (major isomer) and a plausible transition state for cyanation with Et_2AlCN in the one-pot reaction

Our β-cyanohydroxymethyl α-amino acid products can be readily transformed to hydroxyglutamic acid derivatives (**4** and **5**) and hydroxyornithine derivatives (**6** and **7**) bearing

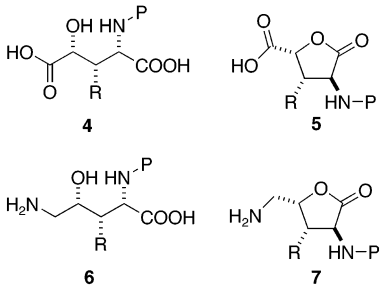


Figure 2. Hydroxyglutamic acid derivatives (**4** and **5**) and hydroxyornithine derivatives (**6** and **7**) are readily prepared from β-cyanohydroxymethyl α-amino acid derivatives. P = protective group or H.

an alkyl substituent via cyano group hydrolysis[7] and reduction,[7b,9] respectively. Although hydroxyglutamic acid[17]

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(11) Other cyanation conditions, for example, use of TMSCN with or without catalytic amount of $ZnBr_2$, provided diastereomer(s) of **1b** or of the TMS-form of **1b**, respectively.

(12) See Supporting Information.

(13) Cyanohydrin **1b** was also gradually converted to lactone **2b** without any reagent. When **1b** was stirred in EtOAc or in THF at room temperature, formation of **2b** was observed after 24 h.

(14) The stereochemistries of **1a**, **1c**−**h**, **2a**, and **2c** were determined by analogy.

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and hydroxyornithine[18] are important compounds, synthetic approaches to such alkyl-substituted versions are rare.[19] Our methodology provides ready access to these compounds. Further, our recent discovery that (*S*)-2-methoxymethylpyrrolidine (SMP) catalyzes direct asymmetric Mannich-type reactions of unmodified aldehydes with *N*-PMP-protected α-imino ethyl glyoxylate in a highly *anti*-selective manner (dr up to 19:1) with high enantioselectivity suggests that a wide range of *β*-cyanohydroxymethyl α-amino acid stereoisomers and their derivatives can be readily accessed. [3c]

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In summary, we have demonstrated that L-proline-catalyzed Mannich-type reactions followed by cyanation with Et_2AlCN provides in one pot highly enantiomerically pure cyanohydrin-functionalized α-amino acid derivatives bearing three contiguous stereogenic centers. These results indicate that aldehyde products of L-proline-catalyzed Mannich-type reactions can be efficiently used for further reactions without purification. Additional applications of this one-pot strategy are currently underway in our laboratory.

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Supporting Information Available: Complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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