An Improved Stereoselective Synthesis of *threo*-β-Hydroxyamino Acids[1]

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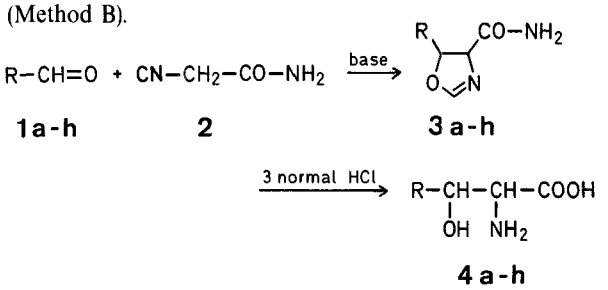
In recent years, reactions using isonitrile compounds have exploited new types of synthetic methods for α-amino acids[2,3,4]. For example, reaction of α-isocyanoacetic acid derivatives with aldehydes is a useful stereoselective synthesis of β-hydroxyamino acids which are a biologically important class of amino acids[5-9]. In a previous paper[10], a general synthetic method for β-hydroxyamino acids by reaction of *N*-substituted α-isocyanoacetamide with aldehydes was reported; nevertheless, milder conditions for the cleavage of the amide bond are still desired. In this paper, an improved method using α-isocyanoacetamide, which is susceptible to acid hydrolysis, as a starting material is described.

α-Isocyanoacetamide (**2**) was easily prepared in a 95% yield by a treatment of methyl α-isocyanoacetate with methanolic ammonia. The reaction of isocyanoacetamide (**2**) with aldehydes **1** proceeded to afford *trans*-oxazoline-4-carboxamide **3**, the thermodynamically more stable isomer[9], in the presence of alkali metal bases such as potassium hydroxide and sodium carbonate, as shown in the Scheme. When the intermediate **3** was obtained as crystals, it was purified by recrystallization and then the pure *trans*-oxazoline **3** was hydrolyzed with 3 normal hydrochloric acid to *threo*-β-hydroxyamino acid **4** (Method A). In the case of non-crystalline oxazolines **3** the reaction mixture was directly hydrolyzed with 3 normal hydrochloric acid and the resultant product was treated with an ion exchange resin followed by recrystallization to give the pure *threo*-β-hydroxyamino acid **4** (Method B).



α-*Isocyanoacetamide* (**2**); yield: 95%; m.p. 122–123° (methanol).

I.R. (nujol): ν_{max} = 3350, 3300, 3250, 2170, 1670, 1605 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 4.28 (s, 2H, CH_2); 7.4 ppm (br., 2H, NH_2).

***threo*-β-Hydroxyamino Acids 4; Typical Procedures:**

Method A: To a stirred solution of potassium hydroxide (85% purity; 1.98 g, 0.03 mol) in methanol (10 ml) is added a mixture of **2** (2.52 g, 0.03 mol) and benzaldehyde (**1f**; 3.50 g, 0.033 mol) in methanol (10 ml) at 10–15°. After being stirred for 2 h at the same temperature, the reaction mixture is allowed to stand in a refrigerator overnight. The resultant crystals are collected by filtration and washed with ether. Recrystallization from methanol affords trans-*5-phenyl-2-oxazoline-4-carboxamide* (**3f**); yield: 4.8 g (84%); m.p. 117–123° (sublimation).

$C_{10}H_{10}N_2O_2$	calc.	C 63.15	H 5.30	N 14.73
(190.2)	found	63.05	5.31	14.52

I.R. (nujol): ν_{max} = 3400, 3260, 3120, 1700, 1640 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 4.37 (dd, 1H, 4-C—H, J = 7.5 Hz, 2.25 Hz); 5.54 (d, 1H, 5-C—H, J = 7.5 Hz); 7.1–7.5 ppm (m, 8H, 2-C—H + C_6H_5 + NH_2).

trans-*5-(4-Nitrophenyl)-2-oxazoline-4-carboxamide* (**3g**) is obtained similarly; yield: 88%; m.p. 162–163° (dec., from methanol).

$C_{10}H_9N_3O_4$	calc.	C 51.06	H 3.86	N 17.87
(235.2)	found	51.15	3.93	17.76

I.R. (nujol): ν_{max} = 3460, 3280, 3200, 1680, 1635, 1600 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 4.37 (dd, 1H, 4-C—H, J = 7.5 Hz, 2.25 Hz); 5.68 (d, 1H, 5-C—H, J = 7.5 Hz); 7.46 (d, 1H, 2-C—H, J = 2.25 Hz); 7.2–7.5 (br, 2H, NH_2); 7.57, 8.25 ppm (A_2B_2 q, 4H_{arom}, J = 8.25 Hz).

To the oxazoline **3f** (3.80 g, 0.02 mol) is added 3 normal hydrochloric acid (20 ml) and the mixture is heated at 70–80° for 2 h. The solution is evaporated to dryness in vacuo and the residue

Table. Preparation of *threo*-β-Hydroxyamino Acids **4a–h**

Product[a]	R	Reaction conditions base/solvent	Yield[b] [%]	m.p. (dec.)	Lit. m.p. (dec.)	Molecular formula[f]
4a	H	Na_2CO_3/H_2O	90	228–236°	234–244°[13]	$C_3H_7NO_3$ (105.1)
4b	CH_3	KOH/CH_3OH	89[c]	184–190°	—	$C_4H_9NO_3$ (119.1)
4c	C_2H_5	KOH/CH_3OH	87	214–215°	227–228°[14]	$C_5H_{11}NO_3$ (133.2)
4d	*i*-C_3H_7	KOH/CH_3OH	90	225–228°	227°[15]	$C_6H_{13}NO_3$ (147.2)
4e	HOOC	$NaOH/CH_3OH/H_2O$	68	250–262°	>235°[16]	$C_4H_7NO_5$ (149.1)
4f	C_6H_5	KOH/CH_3OH	80	194–195°	193–194°[15]	$C_9H_{11}NO_3$ (181.2)
4g	4-O_2N—C_6H_4	KOH/CH_3OH	84	182–185°	188°[17]	$C_9H_{10}N_2O_5$ (226.2)
4h	3-pyridyl	KOH/CH_3OH	72	222–232°[d]	219–220°[e,18]	$C_8H_{12}Cl_2N_2O_3$ (255.1)

[a] Products were homogeneous by P.P.C.[11] and ^{1}H-N.M.R.[12,18].
[b] Yield based on **2**. Recrystallization from H_2O/CH_3OH.
[c] *threo*; *erythro* ratio = 85:15 by ^{1}H-N.M.R.
[d] Dihydrochloride.
[e] Monohydrochloride.
[f] The microanalyses for all products were in satisfactory agreement with the calculated values (C ±0.18, H ±0.10, N ±0.16, Cl ±0.11).

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is dissolved in methanol (10 ml). The solution is neutralized with concentrated ammonia. The resultant crystals are collected by filtration and washed with methanol and ether. Recrystallization from water affords threo-β-*phenylserine* (**4f**); yield: 3.44 g (95%); m.p. 194–195° (dec.).

By the same treatment, threo-β-*(4-nitrophenyl)-serine* (**4g**) was obtained; yield: 95%; m.p. 182–185° (dec.).

Method B: To a stirred solution of sodium hydroxide (0.8 g, 0.02 mol) in water (5 ml) is added a mixture of **2** (1.68 g, 0.02 mol) and glyoxalic acid hydrate (**1e**; 2.3 g, 0.025 mol) in methanol (10 ml) at 10–15° for 30 min. After stirring is continued for 2 h at room temperature, to the mixture is added 3 normal hydrochloric acid (20 ml), and the mixture is heated at 70–80° for 2 h. The solution is evaporated to dryness in vacuo and the residue is dissolved in water (5 ml). The solution is treated with an ion exchange resin, Amberlite IR 120 ($H^{\oplus}$ form). After washing with water, the amino acid is eluted with 5% ammonia. The eluate is evaporated to dryness in vacuo and the resultant crystals are recrystallized from water to afford threo-β-*hydroxyaspartic acid* (**4e**); yield: 2.03 g (68%); m.p. 250–262° (dec.).

In a similar manner, serine (**4a**), *threo*-theronine (**4b**), *threo*-β-hydroxynorvaline (**4c**), *threo*-β-hydroxyleucine (**4d**), and *threo*-β-(3-pyridyl)-serine (**4h**) were synthesized using formalin, acetaldehyde, propanal, 2-methylpropanal, and 3-formylpyridine, respectively. The physicochemical properties of these amino acids obtained were in accord with those of authentic speciemens. The reaction conditions and yields are summarized in the Table.

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