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Syntheses and Biological Activities of Isonitrile Dipeptides

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Note

Syntheses and Biological Activities of Isonitrile Dipeptides[1]

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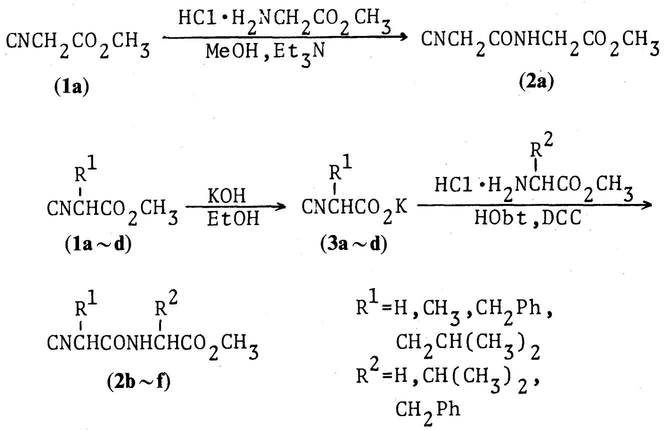
In the course of our studies to develop medicines and agricultural chemicals from amino acids, we have been paying attention to the peculiar reactivities[2] and biological activities of isocyano (isonitrile) compounds.[3]

We reported in the previous paper[4] that a variety of α-isocyanoacetic acid derivatives, which are amino acid analogs, exhibited considerably strong inhibitory activities to germination of some seeds. Of these, the α-isocyanoacetic acid amide compounds especially showed almost same effects as 2,4-dichlorophenoxyacetic acid (2,4-D) as a standard agent.

In the succeeding study, we had great interest in peptide compounds containing the isocyano group. Furthermore, from a chemical viewpoint, isonitrile peptides seem to be useful in the four-component condensation (4CC) peptide synthesis.[5] Nevertheless, only one synthetic method, which involved dehydration of the *N*-formyl peptides using phosgene[6] or tosyl chloride[7] in the presence of a base, is known to date. On the other hand, with regard to the synthesis of an amide compound containing the isonitrile group, we previously reported the direct amidation of isocyanoacetates with primary or cyclic amines.[8]

In this study, we first extended the amidation to the synthesis of isonitrile peptides using amino acid esters as amine components. Consequently, *N*-isocyanoacetylglycine methyl ester (**2a**), which is the most simple of isonitrile dipeptides, was afforded in a 25.6% yield after stirring for 2 days. However, the coupling reaction using such bulky amino acid esters as valine or phenylalanine scarcely proceeded, the starting materials being almost fully recovered or only tarry products being obtained. We then attempted one step condensation based on the usual peptide coupling method using potassium α-isocyanoacetate (**3**). Concerning the use of potassium α-isocyanoacetate, Hoppe has reported that the coupling reaction with amino acids in dimethyl sulfoxide at 100°C gave the potassium salt of *N*-formyl dipeptides.[9] It was suggested that the reaction would proceed through oxazolinone *via* α-isocyanoacetic acid. From the view point of preventing the formation of the oxazolinone compound, we investigated a variety of active ester coupling methods. As a result, the reaction of potassium isocyanoacetate (**3a**) with L-valine methyl ester hydrochloride, using dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HObt) in acetonitrile (CH_3CN), proceeded easily and the desired corresponding *N*-isocyanoacetyl-L-valine methyl ester (**2b**) was obtained in a good yield. In the same way, various isonitrile peptide compounds (**2c**~**f**) were synthesized and confirmed by IR or NMR spectra and elemental analyses. These results are summarized in Table I. In this method, HObt and CH_3CN should be essential, since *N*-acylurea was exclusively obtained in the use of other solvents such as tetrahydrofuran or chloroform. Furthermore, in the absence of HObt the yields of the peptides (**2**) were very low.



Scheme 1.

TABLE I. YIELDS, PHYSICAL PROPERTIES, AND ANALYTICAL DATA OF ISONITRILE PEPTIDES (**2**)

Compd. No.	R^1	R^2	Yield (%)	mp (°C)	$[\alpha]_D^{25}$ (c1, MeOH)	IR ν_{max}^{Nujol} cm^{-1}	NMR (in $CDCl_3$) δ OCH_3[a]	NMR (in $CDCl_3$) δ NH[b]
2a	H	H	25.6	92~94	—	3310, 2170, 1745, 1670	3.76[c]	7.9~8.4
2b	H	$CH(CH_3)_2$	55.6	76~78	−27.2°	3350, 2150, 1748, 1740, 1655	3.75	7.5~8.1
2c	H	CH_2Ph	52.9	96~98	+17.1°	3320, 2160, 1747, 1730, 1670	3.77	6.6~7.1
2d	CH_3	H	60.5	Oil	—	3300, 2140, 1745,[d] 1675	3.80	6.8~7.3
2e	$CH_2CH(CH_3)_2$	H	53.8	62~64	—	3270, 2140, 1750, 1670	3.79	6.8~7.4
2f	CH_2Ph	H	56.9	84~86	—	3300, 2150, 1740, 1665	3.77	6.85~7.15

[a] Singlet. [b] Broad. [c] Taken in $CDCl_3+d_6$-DMSO. [d] Taken in film.

TABLE II. INHIBITORY ACTIVITIES AGAINST GERMINATION BY ISONITRILE PEPTIDES (**2**)

Compd. No.	Rice plant 100 ppm stem	Rice plant 100 ppm root	Rice plant 10 ppm stem	Rice plant 10 ppm root	Cucumber plant 100 ppm stem	Cucumber plant 100 ppm root	Cucumber plant 10 ppm stem	Cucumber plant 10 ppm root	Radish plant 100 ppm stem	Radish plant 100 ppm root	Radish plant 10 ppm stem	Radish plant 10 ppm root
2a	−	−	−	−	±	±	−	−	−	−	−	−
2b	+	+	−	−	+	+	±	+	−	±	−	−
2d	−	−	−	−	±	±	−	±	±	±	−	−
2e	−	±	−	−	+	+	−	±	+	+	−	−

−, no effect against germination; ±, 50~80% inhibition of growth for seedlings; +, 80~100% inhibition of growth for seedlings.

The *N*-(α-isocyanoacetyl)amino acid methyl esters (**2**) thus obtained were tested for their inhibitory activities against the germination of rice, radish, and cucumber seeds according to Koaze's method as previously reported.[10] The activities of the isonitrile peptides at concentrations of 100 and 10 ppm are summarized in Table II, and these compounds did not exhibit such marked effects on germination as the α-isocyanoacetic acid amide derivatives reported.[4] *N*-Isocyanoacetyl-L-valine methyl ester (**2b**), which showed the most potent activity of these, inhibited 80~100% against the germination of rice and cucumber seedlings at the concentration of 100 ppm, but exhibited little activity at 10 ppm.

EXPERIMENTAL[11]

Potassium α-Isocyanoacetates. Methyl esters (**1a**~**d**) were treated with potassium hydroxide according to a method similar to that described in the previous paper.[4] Yields and physical properties of new compounds are as follows.

Potassium 2-Isocyano-4-methylpentanoate (**3c**): Yield 72.1%, mp 196~198°C. IR ν_{max}^{Nujol} cm^{-1}: 2140 and 1600.

Potassium 2-Isocyano-3-phenylpropionate (**3d**): Yield 75.4%, mp 193~195°C. IR ν_{max}^{Nujol} cm^{-1}: 2160 and 1620.

Synthesis of N-Isocyanoacetylglycine Methyl Ester (**2a**) *(Direct Amidation).* A solution of methyl isocyanoacetate (**1a**, 3 g, 30 mmol), glycine methyl ester hydrochloride (5.65 g, 45 mmol), and triethylamine (6.3 ml, 45 mmol) in methanol (30 ml) was stirred for 2 days at room temperature. The solution was treated as described in the previous paper[4] to give the title compound as colorless crystals (1.2 g, 25.6%). Found: C, 45.97; H, 5.20; N, 18.10; Calcd. for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94%.

Typical Procedure for the Direct Coupling—Synthesis of N-Isocyanoacetyl-L-valine Methyl Ester (**2b**). L-Valine methyl ester hydrochloride (1.68 g, 10 mmol), HObt (1.35 g, 10 mmol), and DCC (2.06 g, 10 mmol) were added to a suspension of potassium isocyanoacetate (**3a**, 1.23 g, 10 mmol) in CH_3CN (20 ml) under ice cooling. The reaction mixture was stirred for 1 hr at the same temperature and ethyl acetate (AcOEt) (20 ml) was added to the mixture. The insoluble materials were filtered off and the filtrate was washed with 0.5 M aqueous citric acid, saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$, and then concentrated to dryness. The crystals obtained were isolated by suction and washed with diisopropyl ether. Recrystallization from AcOEt–hexane gave **2b** as colorless crystals (1.1 g, 55.6%), NMR (in $CDCl_3$) δ: 0.95 (6H, d, $J=6$ Hz, $2\times CH_3$), 1.7~2.1 [1H, m, $\underline{CH}(CH_3)_2$], 3.75 (3H, s, OCH_3), 4.28 (2H, s, CH_2), 4.3~4.6 (1H, m, NCH), and 7.5~8.1 (1H, m, NH). Found: C, 54.51; H, 7.12; N, 14.13; Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13%.

Germination Test. The following seeds were used in the test; rice plant, Nihon-masari harvested in Saitama Pref.; cucumber, Shinjibae harvested in the field of Nohara Seed Co., Ltd.; and radish, Kotomaru Shogoin harvested in the field of Takayama Seed Co., Ltd. The germination tests were carried out according to the method reported by Koaze *et al.*[10] and ourselves.[4]

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11) Melting points were measured by a Yamato melting point apparatus and are uncorrected. The specific rotations were obtained with a Perkin-Elmer 243 polarimeter. IR spectra were recorded with a Shimadzu IR-27G spectrophotometer and NMR spectra with a Hitachi Perkin-Elmer R-20A high resolution NMR spectrometer using tetramethylsilane as an internal standard. Column chromatography was carried out on silica gel (Kieselgel 60, 0.063~0.200 mm, E. Merck).