THE SYNTHESIS OF L- α -AMINONITRILES

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N-o-Nitrophenylsulfenyl(NPS)-L- α -amino acid(alanine, leucine, and phenylalanine) amides were dehydrated in POCl₃-pyridine to yield the corresponding NPS-L- α -aminonitriles, which gave the L- α -aminonitrile hydrochlorides by treatment with anhydrous HCl. Optical purity of these nitriles was well retained.

 α -Aminonitriles can be synthesized by the reaction of ammonium cyanide with the carbonyl compounds, that is known as Zelinsky-Stadnikoff synthesis 1) and yields always the racemic products. The purpose of this study is to synthesize enantiomeric α -aminonitriles from the corresponding α -amino acids as starting materials. Several investigators 2-6) have reported on the preparation of N-protected α -aminonitriles by dehydrating the corresponding amino acid amides. They used the benzyloxycarbonyl, the phthalyl or the acetyl as an N-protecting group. These N-protecting groups have not been removed.

In the previous paper $^{7)}$ alanyl- α -aminopropionitriles have been synthesized by the dehydration of the corresponding NPS-dipeptide amides, followed by treatment with anhydrous HCl. In this paper, this method was employed for the preparation of L- α -aminonitriles as follows:

$$\begin{array}{c} R \\ \text{NPS-NH-CH-CONH}_2 \\ \text{(I)} \end{array} \xrightarrow{\begin{array}{c} \text{POCl}_3-\text{Pyridine} \\ \text{CH}_3 \end{array}} \xrightarrow{\text{NPS-NH-CH-CN}} \xrightarrow{\begin{array}{c} \text{HCl} \\ \text{R} \end{array}} \xrightarrow{\begin{array}{c} \text{R} \\ \text{H_2N-CH-CN} \end{array}} \xrightarrow{\text{HCl}} \\ \text{(II)} \end{array} \xrightarrow{\text{CH}_3} \text{(III)} \xrightarrow{\text{CH}_1 \times \text{HCl}}$$
 a: R= CH₂-CH₂, b: R= CH₂-CH_{CH₃}, c: R= CH₂- ϕ , NPS: o-Nitrophenylsulfenyl

Ia was obtained easily by the ammonolysis of the corresponding methyl ester in methanol saturated with ammonia. However, the ammonolysis of methyl-N-NPS derivatives of leucine and phenylalanine did not proceed under the same conditions. Therefore, Ib and Ic were prepared by the reaction of the amino acid amides with o-nitrophenyl-sulfenyl chloride. The NPS-amino acid amides(Ia-c) were dehydrated in cold POCl₃-pyridine 7) to yield the corresponding nitriles(IIa-c). When these products were treated with anhydrous HCl in ethyl acetate or ethyl ether, the α -aminonitrile hydrochlorides(IIIa-c·HCl) precipitated, which are summarized in Table 1. They were identified with elemental analyses and IR spectra. When they were chromatographed with an amino acid analyzer, IIIa and IIIc were eluted more rapidly than the corresponding amides. Though IIIb and leucine amide were not separated by this chromatography, they were separated by paper chromatography. The Rf values of these α -aminonitriles on paper chromatography are also shown in Table 1. Any extra spot due to impurity was not observed.

Table 1. Yields and Physical Properties of L- α -Aminonitrile Hydrochlorides

	α -Aminonitrile·HCl	Mp°C(decomp.)	Yield(%)	$a [\alpha]_D^{22}(deg.)$	νC≡N(cm ⁻¹)	Rf ^c
•	IIIa	156-158	13	-15.3(c 0.708,H ₂ 0)	2260	0.55(0.49) ^d
	IIIb	173-176	76	+13.5(c 0.487,H ₂ 0)	2260	$0.86(0.69)^{d}$
	IIIc	176-178	30	+5.8(c 0.790,H ₂ 0)) 2250	$0.84(0.70)^{d}$

a) Calculated on the basis of I. b) Measured as KBr tablet. c) Paper chromatography was carried out on Toyo Filter Paper No. 50 using the solvent system of n-BuOH-AcOH- $H_2O(4:1:2 \text{ v/v})$. d) R_f value of the corresponding amide.

Retention of configuration in the L- α -aminonitriles(IIIa-c) was examined by a gas chromatographic method. 8) These compounds were transformed into the amino acid methyl esters by treatment with 9N HCl-methanol, followed by addition of a small amount of water. These methyl esters were transesterified in (+)-2-butanol saturated with anhydrous HCl to give the (+)-2-butyl esters, which were then trifluoroacetylated with (CF₃CO)₂O. The N-trifluoroacetyl(TFA)-amino acid (+)-2-butyl esters obtained were analyzed by gas chromatography on the capillary column coated with LB 550X. The N-TFA-DL and L-amino acid (+)-2-butyl esters which were derivatized from DL and L-amino acids(alanine, leucine and phenylalanine) respectively, were also analyzed.

Table 2. Steric Purity of L- α -Aminonitriles

	Retention time(min.)		Apparent	Apparent steric purity				
α-Aminonitrile	of diast L-(-)	tereomers ^a L-(+)	steric purity L/(D+L)	of standard sample ^b L/(D+L)				
IIIa	12.2	13.0	0.93	0.93(L-alanine)				
IIIb	21.8	22.8	0.93	0.93(L-leucine)				
IIIc	64.0	64.8	0.94	0.92(L-phenylalanine)				

a) Gas chromatography were carried out with a Hitachi gas chromatograph 063 provided with a flame ionization detector. Column: 150 ftx0.01 in. stainless steel capillary column(LB 550X), temperature 100-170°C 1°C/min; carrier gas He, 4.1Kg/cm²; H₂, 1.5Kg/cm². b) The standard samples were prepared by derivatization of commercial L-amino acids(Guaranteed Reagent).

The diastereomers of N-TFA-DL-amino acid (+)-2-butyl esters had almost identical detector responce. Since the (+)-2-butanol⁹⁾ used in this work contained a small amount of (-)-isomer, the N-TFA-amino acid (+)-2-butyl ester derivatized from each L-amino acid was found to contain a small amount of L-(-) diastereomer. The N-TFA-amino acid (+)-2-butyl ester derivatized from each L- α -aminonitrile, also contained a small amount of L-(-) diastereomer. The gas chromatographic data are summarized in Table 2, which shows that the apparent steric purity of each L- α aminonitrile is almost identical with that of the standard L-amino acid. This indicates that the optical purity of the L-lpha-aminonitriles(IIIa-c) is well retained. Though their yields are rather poor, the method described above may be useful for the synthesis of enantiomeric α -aminonitriles.

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