EFFICIENT SYNTHESIS OF 1-SUBSTITUTED 2,5-DICYANOPYRROLIDINES BY THE STRECKER REACTION USING SUCCINALDEHYDE AND PRIMARY AMINES, AND THEIR STEREOCHEMISTRY

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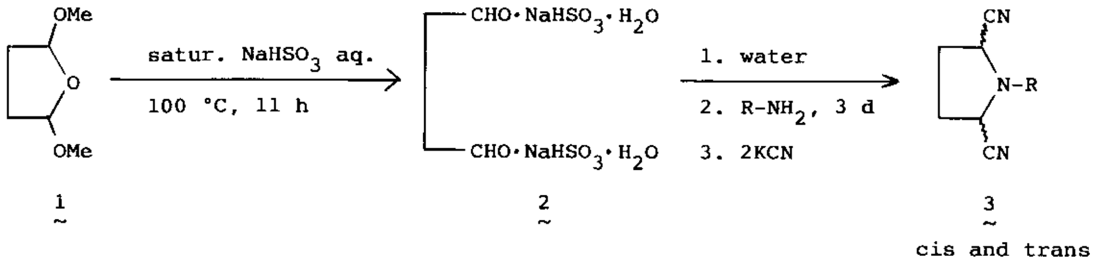
Abstract —— An efficient sequence proposed here for new synthesis of 1-substituted 2,5-dicyanopyrrolidines involves the simple Strecker reaction using succinaldehyde bis-sodium bisulfite and primary amines. Furthermore, their stereochemistry is also discussed.

α-Aminonitriles are known to be synthetically equivalent to a carbonyl group[1] and important as masked acyl anion eqiivalents in the formation of C-C bonds[2]. In our previous papers[3,4], a preparative method and the synthetic utility of 1-substituted 2,6-dicyanopiperidines, which are cyclic α-aminonitriles, were reported. However, there is no information on a synthetic method of 1-substituted 2,5-dicyanopyrrolidines. We report here that the Strecker reaction of succinaldehyde with primary alkyl- and arylamines affords 1-substituted 2,5-dicyanopyrrolidines (3) in good yields, and we also discuss their stereochemistry.

An efficient sequence for the synthesis of 3 involves the simple reactions depicted in Scheme 1: Firstly, preparation of succinaldehyde bis-sodium bisulfite dihydrate (2) was carried out by heating a mixture of 2,5-dimethoxytetrahydrofuran (1) and saturated sodium hydrogensulfite solution according to the reported procedure[5]. Isolated 2 (34.4 g, 0.1 mol) was then dissolved in 850 ml of water, and an aqueous solution (150 ml) of the primary alkyl- or arylamine (0.1 mol) was added dropwise to the solution at room temperature under a nitrogen atmosphere. After the solution was stirred for 3 days, addition of powdery potassium cyanide (13.0 g, 0.2 mol) gave 3 in good yield. For example, when methylamine was used, 1-methyl-2,5-dicyanopyrrolidine (3a) was obtained in 86% yield. Likewise, when

Scheme 1. Preparation of 2,5-dicyanopyrrolidines **3**



a : R= CH_3
b : R= C_2H_5
c : R= n-C_4H_9
d : R= $CH_2C_6H_5$
e : R= $CH_2CH_2C_6H_5$
f : R= p-$CH_3OC_6H_4$
g : R= iso-C_3H_7
h : R= C_6H_5

ethyl-, n-butyl-, benzyl-, phenethyl-, and isopropylamines and aniline were used, 1-ethyl-, 1-n-butyl-, 1-benzyl-, 1-phenethyl-, 1-isopropyl-, and 1-phenyl-2,5-dicyanopyrrolidines (**3b**, **3c**, **3d**, **3e**, **3g**, and **3h**, respectively) were obtained in 56-98% yields. p-Anisidine which is solid and insoluble in water, was used after being transformed to water-soluble p-methoxyanilinium hydrogensulfite, but the formation of 1-(p-methoxyphenyl)-2,5-dicyanopyrrolidine (**3f**) was resulted in low yield (26%).

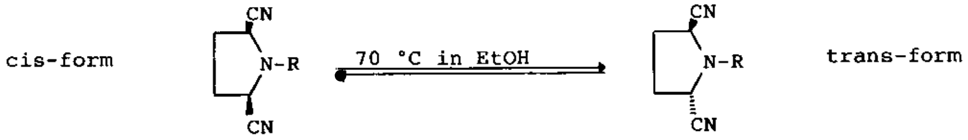
Except the case of **3h** which gave only the cis-isomer, all pyrrolidines **3** obtained in this work were prepared as a mixture of cis- and trans-isomers. The configurational determination of five-membered rings are generally difficult[6]. However, the configurations of the two cyano groups of each stereoisomer were examined by ^1H-NMR (270 MHz) (see Table). Pyrrolidines such as **3b**, **3c**, **3d**, and **3e**, which possess a methylene group directly situated on the nitrogen atom, provide definitive evidence for the difference between cis and trans structural assignments: The methylene protons of the cis-isomer are equivalent, while those of the trans-isomer are unequivalent, giving rise to two distinguishable doublets with a coupling constant of about 13 Hz, which is similar to that reported for trans-1-benzyl-2,6-dicyanopiperidine[3]. For example, in the case of **3d**, the equivalent benzyl methylene protons of the cis-form give a singlet at δ 4.08, and the unequivalent those of the trans-form give two doublets with a coupling constant of 13

Hz at δ 3.66 and 4.30. The similar conclusions are drawn for 3b, 3c, and 3e (see Table). On the other hand, cis- and trans-isomers of 3a, 3f, 3g, and 3h, which do not directly have the methylene group on the nitrogen atom, are not plainly distinguishable by means of ^{1}H-NMR.

Melting points of cis-isomers of 3b, 3d, and 3e, except oily 3c, as well as those of 1-substituted 2,6-dicyanopiperidines[3] are higher than those of the trans-isomer. Additionally, Rf values of cis-isomers are lower than those of trans-isomers. These results are a general observation for all 2,5-dicyanopyrrolidines 3. While Jones and co-workers reported[7] that cis-2,5-dialkylpyrrolidines eluted first by GC/MS, we suggest that these stereoisomers should not be treated by thermal means such as GC because of easy transformation from cis- to trans-pyrrolidines under conditions as described later.

When ^{1}H-NMR spectra look at from the viewpoint of the above proposal, it is generally observed for all pyrrolidines 3, except 3f and 3h which have a magnetically anisotropic benzene ring situated on the nitrogen atom, that cis-methine protons α to the CN group are less shielded from 0.04 to 0.23 ppm than trans-methine protons. On the other hand, the cis-methine protons of 3f and 3h are more shielded, from 0.02 to 0.05 ppm by the magnetic anisotropic effect of the benzene ring, than trans-methine protons. Thus, the apparent unification for differences between cis- and trans-isomers was recognized in the physical properties of melting points, Rf values, and ^{1}H-NMR spectra.

Scheme 2. Thermal interconversion



cis-3b $\xrightarrow{70\ ^\circ\mathrm{C},\ 1\ \mathrm{h}}$ trans-3b (42%)

cis-3b $\xrightarrow{70\ ^\circ\mathrm{C},\ 2\ \mathrm{h}}$ trans-3b (59%)

cis-3c $\xrightarrow{70\ ^\circ\mathrm{C},\ 1\ \mathrm{h}}$ trans-3c (42%)

cis-3c $\xrightarrow{70\ ^\circ\mathrm{C},\ 2\ \mathrm{h}}$ trans-3c (59%)

cis-3h $\xrightarrow{70\ ^\circ\mathrm{C},\ 4\ \mathrm{h}}$ trans-3h (36%)

cis-3h $\xrightarrow{70\ ^\circ\mathrm{C},\ 8\ \mathrm{h}}$ trans-3h (38%)

As the typical examples of thermal interconversion, cis **3b**, **3c**, and **3h** were converted to these trans-forms. Thus, when cis-**3b** in ethanol was heated at 70 °C for 1 h, partial conversion of cis-**3b** to trans-**3b** was confirmed by isolating both cis- (58%) and trans-isomers (42%). When the heating time was 2 h, the conversion ratio of cis : trans was 41% : 59%. Likewise, cis-**3c** was converted to 42% or 59% of trans-**3c** by heating for 1 h or 2 h, respectively. Similary, cis-**3h**, obtained as a single isomer, was converted to 36% or 38% of trans-**3h** by heating 4 h or 8 h, respectively. These results suggest that cis-pyrrolidines **3** are obtained under kinetically-controlled conditions, and thermodynamically converted to trans-pyrrolidines. The facility for the conversion is presumed to be due to the substituent (R) on the nitrogen atom.

The work using **3** as synthetic reagents for the preparation of useful diketones and pyrrolidine alkaloids is in progress, and will be reported in the near future.

EXPERIMENTAL

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. ^{1}H-NMR spectra were determined with a JEOL FX-270 (270 MHz) nuclear magnetic resonance spectrometer using tetramethylsilane as an internal standard. IR spectra were taken with Diffraction Grating Infrared (Japan Spectroscopic Co. LTD., A-202 type). Microanalytical data were obtained using a Perkin-Elmer 240 elemental analyzer.

(I) *Preparation of succinaldehyde bis-sodium bisulfite dihydrate* (**2**). Preparation of **2** was carried out by a procedure reported in the literature[5] as follows: To an aqueous solution (800 ml) of saturated sodium hydrogensulfite was added 2,5-dimethoxytetrahydrofuran (40.0 g, 0.303 mol), and then the solution was heated at 100 °C for 11 h and cooled to room temperature. After adding ethanol (80 ml) to the solution, large amounts of white precipitate appeared. The precipitate was collected, and recrystallized from 60% ethanol. Thus, **2** was obtained in up to 90% yield.

(II) *Preparation of 1-substituted 2,5-dicyanopyrrolidines* (**3**). *Synthesis of 1-n-butyl-2,5-dicyanopyrrolidine* (**3c**) *as the typical example*: To a solution of **2** (34.4 g, 0.1 mol) dissolved in water (850 ml) was added dropwise an aqueous solution (150 ml) of n-butylamine (7.3 g, 0.1 mol) under a nitrogen atmosphere. After the solution was stirred for 3 days at room temperature, powdery potassium cyanide

Table. Physical properties of pyrrolidines ($\underset{\sim}{3}$) prepared

Product $\underset{\sim}{3}$ R	Yield [%]	Isomer [ratio,%]	mp [°C]	Molecular Formular^a	I.R.KBr ν_{CN} [cm^{-1}]	^{1}H-N.M.R.^{b} (CDCl$_3$), δ[ppm] N-C$\underline{H}_2$R^1	^{1}H-N.M.R.^{b} (CDCl$_3$), δ[ppm] C$\underline{H}$(α to CN)
3a R=CH$_3$	86	cis: 45	87.0-88.0	$C_7H_9N_3$ (135.2)	2250	2.67(3H,s,C$\underline{H}_3$)	3.73-3.78(2H,m)
		trans:55	35.5		2230 2240	2.63(3H,s,C$\underline{H}_3$)	3.70-3.74(2H,m)
3b R=C$_2$H$_5$	69	cis: 26	53.0	$C_8H_{11}N_3$ (149.2)	2240	2.96(2H,q,J=7.3Hz)	3.94-4.03(2H,m)
		trans:74	oil		2240(lf) 2260(lf)	2.69(1H,d-q,J=12&7Hz) 3.07(1H,d-q,J=12&7Hz)	3.79-3.82(2H,m)
3c R=n-C$_4$H$_9$	72	cis: 50	oil	$C_{10}H_{15}N_3$ (177.2)	2240(lf)	2.89(2H,t,J=7.7Hz)	3.92-3.97(2H,m)
		trans:50	oil		2240(lf) 2260(lf)	2.67(1H,d-t,J=12&7.7Hz) 2.97(1H,d-t,J=12&7.7Hz)	3.77-3.81(2H,m)
3d R=CH$_2$C$_6$H$_5$	74	cis: 58	75.6	$C_{13}H_{13}N_3$ (211.3)	2230	4.08(2H,s)	3.91-3.96(2H,m)
		trans:42	oil		2230(lf) 2260(lf)	3.66(1H,d,J=13Hz) 4.30(1H,d,J=13Hz)	3.68-3.78(2H,m)
3e R=(CH$_2$)$_2$C$_6$H$_5$	98	cis: 56	80.4	$C_{14}H_{15}N_3$ (225.3)	2240	3.19(2H,t,J=7.3Hz)	3.96-4.02(2H,m)
		trans:44	oil		2240(lf) 2260(lf)	2.92(1H,d-t,J=12&7Hz) 3.27(1H,d-t,J=12&7Hz)	3.77-3.83(2H,m)
3f R=p-MeOC$_6$H$_4$	26	cis: 83	134.5	$C_{13}H_{13}N_3O$ (227.3)	2250		4.46-4.51(2H,m)
		trans:17	130.4-131.4		2220 2250		4.51-4.53(2H,m)
3g R=iso-C$_3$H$_7$	56	cis: 89	113.8-114.3	$C_9H_{13}N_3$ (163.2)	2240	3.24(1H,q-q,J=6.3Hz) NC$\underline{H}$(Me)$_2$	4.05-4.13(2H,m)
		trans:11	54.0		2250	3.07(1H,q-q,J=6.3Hz) NC$\underline{H}$(Me)$_2$	3.91-3.94(2H,m)
3h R=C$_6$H$_5$	75	cis: 100	188.0-189.0	$C_{12}H_{11}N_3$ (197.2)	2240		4.52-4.56(2H,m)
		trans:0^c	161.5-163.0		2250		4.57-4.59(2H,m)

a. Satisfactory microanalyses obtained; C±0.30, H±0.19, N±0.25.
b. Measured by N.M.R. spectrometer (270 MHz).
c. Obtained after equilibration experiment (see Text).

(13.0 g, 0.2 mol) was added, and stirred for 6 h, then the solution was extracted with dichloromethane (4 x 150 ml). The combined organic layers were dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified by means of column chromatography (silica gel/benzene). Trans-**3c** (6.43 g) eluted first, and cis-**3c** (6.33 g) later. Thus, **3c** was obtained in 72% yield (12.76 g). Other pyrrolidines **3** were also obtained in a similar manner. These physical properties are summarized in Table.

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