

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

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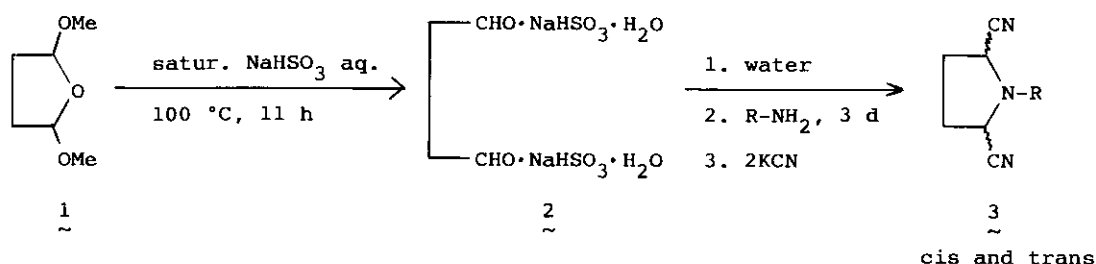
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Abstract — An efficient sequence proposed here for new
synthesis of 1-substituted 2,5-dicyanopyrrolidines involves
the simple Strecker reaction using succinaldehyde bis-sodium
bisulfite and primary amines. Furthermore, their stereo-
chemistry is also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

α -Aminonitriles are known to be synthetically equivalent to a carbonyl group¹ and
important as masked acyl anion equivalents in the formation of C-C bonds². In our
previous papers^{3,4}, a preparative method and the synthetic utility of 1-substi-
tuted 2,6-dicyanopiperidines, which are cyclic α -aminonitriles, were reported.
However, there is no information on a synthetic method of 1-substituted 2,5-di-
cyanopyrrolidines. 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 pro-
cedure⁵. 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= CH₃

b : R= C₂H₅

c : R= n-C₄H₉

d : R= CH₂C₆H₅

e : R= CH₂CH₂C₆H₅

f : R= p-CH₃OC₆H₄

g : R= iso-C₃H₇

h : R= C₆H₅

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%).

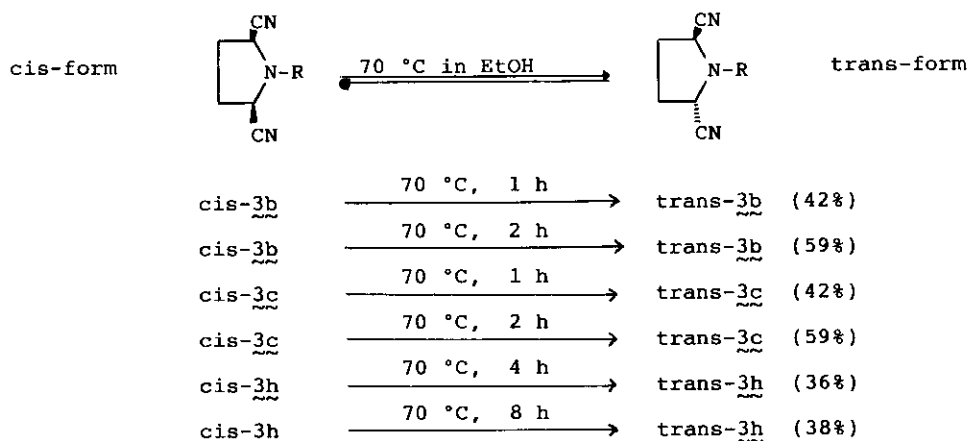
Except the case of 3h which gave only the cis-isomer, all pyrrolidines 3 obtained in this work were prepared as a mixture of cis- and trans-isomers. The configurational determination of five-membered rings are generally difficult⁶. However, the configurations of the two cyano groups of each stereoisomer 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-dicyanopiperidine³. 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 $^1\text{H-NMR}$.

Melting points of cis-isomers of 3b, 3d, and 3e, except oily 3c, as well as those of 1-substituted 2,6-dicyanopiperidines³ 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 reported⁷ 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 $^1\text{H-NMR}$ 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 $^1\text{H-NMR}$ spectra.

Scheme 2. Thermal interconversion



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. Similarly, 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. ¹H-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 literature⁵ 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 (3) prepared

Product 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-CH ₂ R ¹	CH (α to CN)
3a R=CH ₃	86	cis: 45	87.0-88.0	C ₇ H ₉ N ₃ (135.2)	2250	2.67 (3H, s, CH ₃)	3.73-3.78 (2H, m)
		trans: 55	35.5		2230 2240	2.63 (3H, s, CH ₃)	3.70-3.74 (2H, m)
3b R=C ₂ H ₅	69	cis: 26	53.0	C ₈ H ₁₁ N ₃ (149.2)	2240	2.96 (2H, q, J=7.3Hz)	3.94-4.03 (2H, m)
		trans: 74	oil		2240 (1f) 2260 (1f)	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 (1f)	2.89 (2H, t, J=7.7Hz)	3.92-3.97 (2H, m)
		trans: 50	oil		2240 (1f) 2260 (1f)	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 (1f) 2260 (1f)	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 (1f) 2260 (1f)	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 ₃ O (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 ₉ H ₁₃ N ₃ (163.2)	2240	3.24 (1H, q-q, J=6.3Hz) NCH(Me) ₂	4.05-4.13 (2H, m)
		trans: 11	54.0		2250	3.07 (1H, q-q, J=6.3Hz) NCH(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 $\pm$ 0.30, H $\pm$ 0.19, N $\pm$ 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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