Chem. Pharm. Bull. 25(10)2689—2691(1977)

UDC 547.239.2.04 : 524.942.4.04 : 541.63

Stereochemical Studies. L.[1] Reductive Decyanization of α-Amino Nitriles with Sodium in Liquid Ammonia. An Alternate Method for the Application to the Asymmetric Synthesis of optically Active Natural Products[2]

Kiyoshi Tomioka, Kenji Koga, and Shun-ichi Yamada

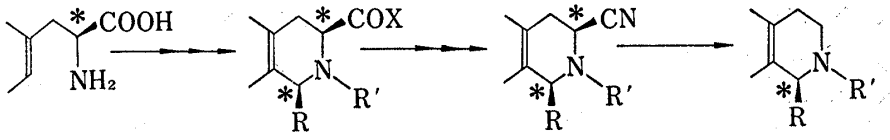
Faculty of Pharmaceutical Sciences, University of Tokyo[3]

(Received February 22, 1977)

An alternate method for reductive decyanization of α-amino nitriles to the corresponding amines was exploited using sodium in liquid ammonia. This method eliminated the limitation encountered in the reaction with sodium borohydride. Using this new process, optically active α-amino nitrile (**8**) was decyanized to **9** without racemization.

Keywords——reductive decyanization; dissolving metal reduction; α-amino nitrile; retention of optical activity; Bredt's rule; sodium in liquid ammonia

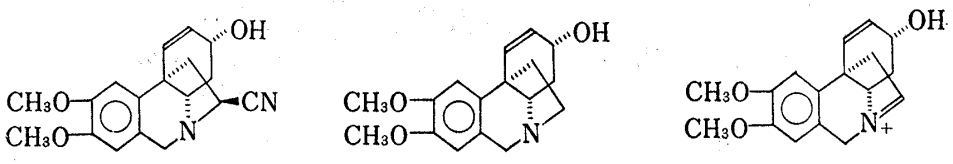
Previous publications[4] from our laboratory have reported a new method for the biogenetic-type asymmetric synthesis of some isoquinoline and indole alkaloids from L-DOPA and L-tryptophan, respectively. This method involves, as a key step, reductive decyanization of α-amino nitrile (**3**) to the corresponding amine (**4**) with sodium borohydride. This step eliminates the original carboxyl group in **1** that has played an important role at the creation of a new asymmetric center in **2**.



1 **2** **3** **4**

Chart 1

Application of this reaction to the α-amino nitrile (**5**) to obtain the corresponding amine (**6**) in the asymmetric synthesis of natural (+)-maritidine from L-tyrosine,[1,5] however, was unsuccessful. Supposing that reductive decyanization of α-amino nitrile with sodium boro-



5 **6** **7**

Chart 2

1) Part XLIX: K. Tomioka, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 2681 (1977).
2) Preliminary communication: S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Lett.*, **1976**, 61.
3) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) *a*) S. Yamada and H. Akimoto, *Tetrahedron Lett.*, **1969**, 3105; *b*) S. Yamada, M. Konda, and T. Shioiri, *ibid.*, **1972**, 2215; *c*) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 2614 (1974); *d*) M. Konda, T. Shioiri, and S. Yamada, *ibid.*, **23**, 1025 (1975); *e*) *Idem*, *ibid.*, **23**, 1063 (1975).
5) S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Lett.*, **1976**, 57.

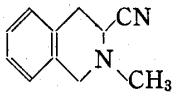
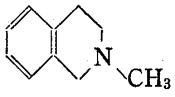
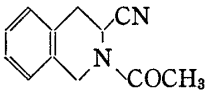
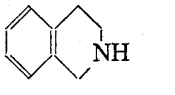
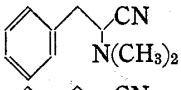
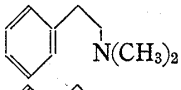
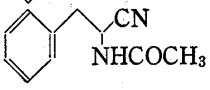
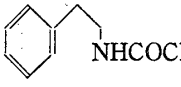
NII-Electronic Library Service

hydride occurrs *via* immonium salt formation, the main reason for the above failure seems to be attributable to the failure in forming the corresponding immonium salt (**7**).[6]

To overcome this limitation, reductive decyanization of α-amino nitrile by sodium metal in liquid ammonia was examined, because formation of hydrocarbons by reductive cleavage of alkyl nitriles with alkali metal-amine or HMPA has already been reported.[7] As the mechanism of this reduction involves radical intermediate, this method is expected to be suitable for the reductive decyanization of α-amino nitriles that are resistant to sodium borohydride method.

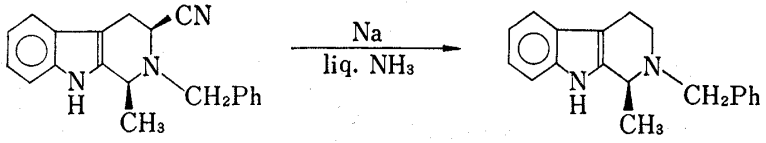
In the present study, α-amino nitrile in tetrahydrofuran was added to a deep blue-colored solution of sodium in liquid ammonia at −78°, and the whole was allowed to stand for 30 min. By the usual work-up, the decyanized product was obtained in an excellent yield as shown in Table I. This reaction condition was found to be highly selective to decyanization, because there was no evidence for the formation of by-products arising from N-benzyl type C-N bond cleavage or Birch reduction.[8]

Table I. Reductive Decyanization of α-Amino Nitriles with Sodium in Liquid Ammonia

α-Amino nitrile	Temp (°C)	Time (min)	Product	Isolated yield (%)
5	−78	15	**6**	58[a]
	−78	20		85
	−78	25		97
	−78	20		95
	−78	30		94

a) Data taken from ref. 5.

Furthermore, to investigate whether racemization at the chiral center in the molecule occurrs under the present reaction condition, optically active α-amino nitrile (**8**)[4a,c] having



8 **9**

Ph=phenyl

Chart 3

6) The failure in formation of compounds with dolble bonds at a bridgehead position is known as Bredt's rule.

7) *a*) P.G. Arapakos, *J. Am. Chem. Soc.*, **89**, 6794 (1967); *b*) P.G. Arapakos and M.K. Scott, *Tetrahedron Lett.*, **1968**, 1975; *c*) P.G. Arapakos, M.K. Scott, and F.H. Huber, *J. Am. Chem. Soc.*, **91**, 2059 (1969); *d*) E.E. van Tamelen, H. Rudler, and C. Bjorklund, *ibid.*, **93**, 7113 (1971); *e*) J.A. Marshall and G.M. Cohen, *J. Org. Chem.*, **36**, 877 (1971); *f*) T. Cuvigny, M. Larcheveque, and H. Normant, *Bull. Soc. Chim. France*, **1973**, 1174; *g*) J.A. Marshall, C.P. Hagen, and G.A. Flynn, *J. Org. Chem.*, **40**, 1162 (1975); *h*) T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *J. Chem. Soc., Perkin I*, **1975**, 737.

8) H.O. House, "Modern Synthetic Reaction," W.A. Benjamin, Inc., Menlo Park, California, 1972, p. 145.

NII-Electronic Library Service

an asymmetric center at easily racemizable benzylic position was decyanized to optically active amine (**9**)[4a,c] with $[\alpha]_D^{27}$ −27.9° (ethanol) in 60% yield. This clearly shows that racemization does not occur during the present decyanization process.

Successful demonstration of reductive decyanization of α-amino nitrile with sodium in liquid ammonia without racemization at the asymmetric center will enable us to perform biogenetic-type asymmetric synthesis of many types of optically active natural products from optically active α-amino acids.

Experimental[9]

General Procedure for Reductive Decyanization——A solution of α-amino nitrile (prepared according to the reported method[4c,10]) (0.5 mmol) in tetrahydrofuran (THF) (3 ml) was added to a deep blue-colored solution of Na (3—4 mg atom) in liquid ammonia (10 ml) at −78° under N_2 atmosphere, and the mixture was stirred for 20—30 min. At the end of this period, excess NH_4Cl was added to decolorize. After the addition of satd. aq. NaCl (10 ml) and $CHCl_3$ (30 ml), ammonia was allowed to evaporate at room temperature. The $CHCl_3$ layer was separated, and the aq. layer was extracted twice with $CHCl_3$ (20 ml each). The combined $CHCl_3$ extracts were washed with water, satd. aq. NaCl, and dried over $MgSO_4$. Evaporation of the solvent afforded the decyanized product, which was compared and identified with the corresponding authentic sample (prepared according to the reported method[4c]) by thin-layer chromatography, gas-liquid chromatography and spectral means infrared spectrum, nuclear magnetic resonance. Results are shown in Table I.

(1*S*)-(−)-2-Benzyl-1-methyl-1,2,3,4-tetrahydro-β-carboline (**9**)——A solution of (1*S*,3*S*)-(+)-2-benzyl-3-cyano-1-methyl-1,2,3,4-tetrahydro-β-carboline (**8**)[11] (150 mg, 0.5 mmol) in THF (3 ml) was added to a deep blue-colored solution of Na (70 mg, 3 mg atom) in liquid ammonia (10 ml) at −78° under N_2 atmosphere, and the mixture was stirred for 25 min. Work-up as described in the general procedure above afforded a pale yellow viscous oil (98 mg), which was purified by alumina column chromatography to give **9** (82.6 mg, 60%) as a colorless oil of $[\alpha]_D^{27}$ −27.9° (c=1.65, EtOH) (reported[4c] $[\alpha]_D^{27}$ −31° (EtOH)).

The hydrochloride was prepared according to the reported[4c] method as colorless fine needles of mp 207—210° (reported[4c] mp 210°).

9) Melting points are uncorrected. Optical rotations were measured with a Yanagimoto Photo Direct Reading Polarimeter.

10) G.R. Clemo and S.P. Popli, *J. Chem. Soc.*, **1951**, 1406.

11) This compound was prepared from L-tryptophan according to the reported method.[4c] Optical rotation value $[\alpha]_D^{20}$ −12.6° (pyridine) in the literature should be read as $[\alpha]_D^{20}$ +12.6° (pyridine).

NII-Electronic Library Service