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REDUCTIVE DECYANIZATION OF α-AMINO NITRILES WITH SODIUM IN LIQUID AMMONIA. USEFULNESS IN ASYMMETRIC SYNTHESES OF OPTICALLY ACTIVE ALKALOIDS

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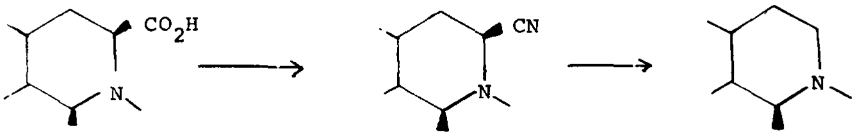
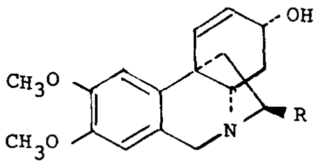
Previous publications[1] from our laboratory have shown that biogenetic-type, asymmetric syntheses of some isoquinoline- and indole-alkaloids are successfully achieved from L-3-(3,4-dihydroxyphenyl)alanine (L-DOPA) and L-tryptophan, respectively. The key step in these asymmetric syntheses is the removal of the carboxyl group in 1 to 3 by reductive decyanization of the intermediate α-amino nitrile (2) with sodium borohydride. Application of this reaction to the α-amino nitrile (4) to obtain 5 in the asymmetric synthesis of (+)-maritidine from L-tyrosine,[2] however, was unsuccessful, probably due to failure in forming the corresponding immonium salt (6).[3] To overcome this difficulty, we investigated



1 2 3



4 R= CN
5 R= H

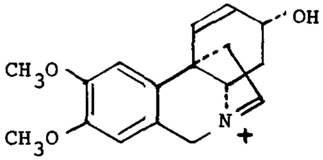


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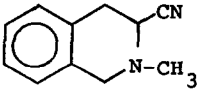
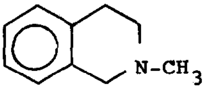
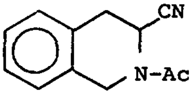
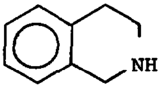
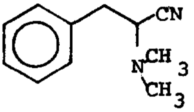
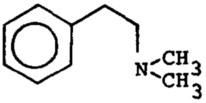
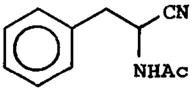
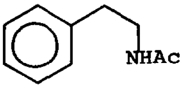
Table. Reductive Decyanization of α-Amino Nitriles with Sodium in Liquid Ammonia-THF

Starting material	Temp(°c)	Time(min)	Product[a]	Yield(%)[b]
4	-78	15	5	58
 (7)	-78	20	 (11)	85
 (8)	-78	25	 (12)	97
 (9)	-78	20	 (13)	95
 (10)	-78	30	 (14)	94

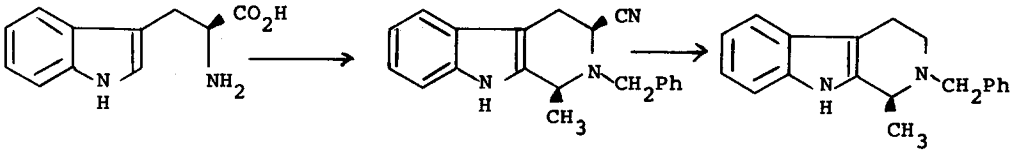
(a) Theses were analyzed by glc and spectral means (ir, nmr). Direct comparisons with authentic samples were made.

(b) Isolated yields.

reductive decyanization of α-amino nitriles with sodium in liquid ammonia-THF and found that 4 afforded 5 in 58% yield in the optically pure state.

Formation of hydrocarbons by reductive cleavage of alkyl nitriles with the alkali metal-amine has been reported.[4] In the present study, α-amino nitrile (0.5 mmoles) in THF (3 ml) was added to a deep blue-colored solution of sodium (4 mg atoms) in liquid ammonia (10 ml) at -78°, and the whole was allowed to stand for 30 min. By the usual sork-up, the decyanized product was obtained in excellent yield as shown in the Table. The selectiveness of this reaction was illustrated by the absence of cleavage of the N-benzyl type C-N bond in 7 and 8. Note that 8 was decyanized to 12, which was not possible with sodium borohydride.

Furthermore, to investigate whether epimerization at the chiral centers in the molecule occurs under these reaction conditions, the α-amino nitrile (16), prepared according to the reported method from L-tryptophan (15)[1a,c,5], was decyanized to 2-benzyl-1-methyl-1,2,3,4-tetrahydro-β-carboline (17) with $[\alpha]_D^{27}$-28° (c=1.65, EtOH) and its hydrochloride mp 207-210° (reported[1c] $[\alpha]_D^{27}$-31° (c=0.7, EtOH), its hydrochloride mp 210°) in 60% yield. This clearly shows that no epimerization occurs during the reductive decyanization process.



15 16 17

Successful demonstration of reductive decyanization of α-amino nitriles with sodium in liquid ammonia without epimerization at the chiral center will enable us to perform biogenetic-type asymmetric syntheses of many types of alkaloids from optically active amino acids.

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