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ASYMMETRIC SYNTHESES OF α-AMINONITRILES VIA CYANOSILYLATION OF SCHIFF BASES

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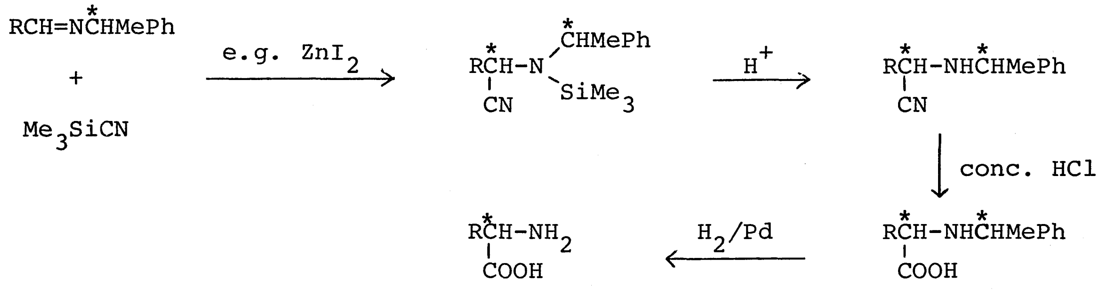
Optically active α-aminonitriles were synthetized by using cyanosilylation of (-)-N-alkylidene-(1-methylbenzyl)amines followed by hydrolysis. The optical yield realized in the reaction was 57.0-69.6 %, which was determined on the basis of nmr spectroscopy.

Recently, it has been shown that trimethylsilyl cyanide(TMSCN) is a good reagent for introducing -C≡N functionality, acylation, protecting and activating carbonyl groups in organic syntheses.[1] However, little attention has been drawn to the reaction of TMSCN with carbon-nitrogen double bonds except our recent report on the formation of 5-TMS-iminodiazolidine-2,4-diones from TMSCN and isocyanates.[2] We found that TMSCN reacted with Schiff bases and oximes in the presence of a catalytic amount of Lewis acid such as $AlCl_3$, ZnI_2, and $Al(OR)_3$ under very mild conditions to afford N-TMS-α-aminonitriles in excellent yields.[3] Now, we wish to report in this communication the effective asymmetric syntheses of α-aminonitriles via cyanosilylation of optically active Schiff bases, (-)-N-alkylidene-(1-methylbenzyl)amines.

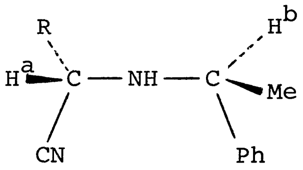
Asymmetric syntheses of α-amino acids have been studied by the use of the reaction of hydrogen cyanide with optically active Schiff bases, followed by hydrolysis and hydrogenolysis. Although the highly optically active(> 98% e.e.) α-amino acids could be obtained,[4] it was shown that the quite high optical purities of these α-amino acids were due to the fractionation during the isolation and purification processes: The attained optical purities of α-amino acids without fractionation were determined to be in a range 22-58% e.e.[5] Obviously, the key-step of the reaction is the asymmetric addition of hydrogen cyanide to the Schiff bases, which affords optically active α-aminonitriles. We found that the optical purities of the α-aminonitriles realized in the asymmetric cyanosilylation of the Schiff bases catalyzed by zinc chloride were much higher than those attained from the cyanation using hydrogen cyanide.

Accordingly, the asymmetric cyanosilylation of the Schiff bases may provide a convenient and powerful route to α-amino acids with high optical purity.[6]

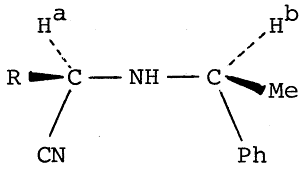


In a typical procedure, 2.50g (25mmol) of TMSCN was added to a mixture of 3.50g (20mmol) of (-)-N-isobutylidene-(1-methylbenzyl)amine and 127mg (2.0 mol%) of zinc chloride at 15-20°C with water bath, and the mixture was stirred for 12 hr. Then the reaction mixture was hydrolyzed by $Et_2O-H_2O-TsOH$ or/and MeOH-TsOH. After the solvent was evaporated the residue was concentrated in vacuo for several hours until the silicon component completely disappeared. Then α-(1-methylbenzyl)amino-isovaleronitrile (4.03g, 99.8%) was obtained, which was spectroscopically pure.

Optical purity of the α-aminonitrile was determined on the basis of 100MHz nmr spectrum: The methine protons(H^a) were employed as key-signal[7] because these protons appeared as well separated doublets (J=6.5HZ) at δ 2.91 and δ 3.37 (84.8:15.2). Thus, the optical purity was determined to be 69.6% e.e.



(S,S) isomer



(R,S) isomer

The configuration of the main diastereoisomer was found to be (S,S) on the basis of the optical rotation in methanol,[4] which was measured for the sample isolated by using column chromatography on silica gel, that was pure enough to satisfy elemental analyses: $[\alpha]^{25}_{D}$ -193.2° (c 2.41 in MeOH), the optical purity determined by nmr was 71.8% e.e. In a similar manner, α-(1-methylbenzyl)aminobutyronitrile, α-(1-methylbenzyl)aminovaleronitrile, and α-(1-methylbenzyl)aminocapronitrile were synthetized. Results are summarized in Table 1.

The optical yields realized in this reaction were found to depend upon the nature of the catalyst employed. For instance, zinc chloride afforded better results than aluminum chloride and aluminum triisopropoxide in this stage. So, we believe that better optical yields can be attained by choosing a catalyst of proper character. Further investigation on the mechanism of the asymmetric induction on this reaction is now in progress.

Table 1 Optically Active α-[(S)-1-methylbenzyl]aminonitriles

R	Yield (%)	$IR(cm^{-1})$[a]	NMR(δ):(H^{a})[b]		Optical Purity(% e.e.)[c]	$[\alpha]^{25}_{D}$[d]
		-C≡N	(S,S)	(R,S)		
CH_3CH_2-	97.0	2225	3.05,t	3.52,t	58.8 (63.4)	-188.1 (70.8)
$CH_3CH_2CH_2-$	98.5	2225	3.08,t	3.56,t	63.5 (68.4)	-163.5 (65.9)
$\begin{matrix}CH_3\\CH_3\end{matrix}{>}CH-$	99.8	2225	2.91,d	3.37,d	69.6 (75.0)	-193.2 (71.8)
$\begin{matrix}CH_3\\CH_3\end{matrix}{>}CHCH_2-$	97.5	2225	3.12,t	3.62,t	57.0 (61.4)	-158.1 (57.6)

a Measured as neat liquid b Measured in $CDCl_3$ by adding D_2O, J=6.5Hz in all cases c Values in parentheses are optical yields which are calibrated by the optical purity of (-)-(S)-(1-methylbenzyl)amine (Norse Laboratories Inc.): $[\alpha]^{25}_{D}$ -37.68 (neat)(lit.[4], $[\alpha]^{25}_{D}$ -40.6), 92.8% purity. d Measured in MeOH (c 1.0-3.2). Values in parentheses are optical purities determined on the basis of nmr specta.

REFERENCES AND NOTES

1. D. A. Evans and L. K. Truesdale, Tetrahedron Lett., 4929 (1973); D. A. Evans, L. K. Truesdale, and G. L. Carroll, Chem. Commun., 55 (1973); D. A. Evans, J. M. Hoffman, and L. K. Truesdale, J. Amer. Chem. Soc., 95, 5822 (1973); W. Lidy and W. Sundermeyer, Chem. Ber., 106, 587 (1973); Idem, Tetrahedron Lett., 1449 (1973).
2. I. Ojima, S. Inaba, and Y. Nagai, Chem. Commun., 826 (1974).
3. I. Ojima, S. Inaba, K. Nakatsugawa, and Y. Nagai, Chem. Lett., 331 (1975).
4. M. S. Patel and M. Worsley, Canadian J. Chem., 48, 1881 (1970).
5. K. Harada and T. Okawara, J. Org. Chem., 38, 707 (1973).
6. Hydrolysis and hydrogenolysis of the α-benzylaminonitriles are well known and established process; see ref. 4 and 5.
7. Fiaud and Horeau [Tetrahedron Lett., 2565 (1972)] reported the estimation of the optical purity of α-(1-methylbenzyl)aminovaleronitrile by means of nmr spectroscopy. They employed the benzyl protons (H^b) of the two diastereoisomers as key-signal for the estimation. However, it seems curious that they did not use the methine protons (H^a) which appeared as well separated triplets (J=6.5 HZ) at δ3.08 for (S,S) isomer and δ3.56 for (R,S) isomer, while the bynzyl protones (H^b) appeared as superimposed quartets (J=6.5 Hz) at δ4.03 for (R,S) isomer and δ4.05 for (S,S) isomer.

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