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LETTERS

Lithium Perchlorate/ Diethylether Catalyzed Aminocyanation of Aldehydes

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Abstract : A simple and efficient one-pot method was developed to give α-aminonitriles from aldehydes + amines + TMSCN in LPDE. Optically active α-aminonitriles were snythesized by using (*S*)-(-)- or (*R*)-(+) α-methylbenzylamine, (*S*)-(-) α-methylbenzylamine affords predominantly *S*-aminonitriles and (*R*)-(+) α-methylbenzylamine leads to the *R*-aminonitriles.

α-Aminonitriles are important intermediates in the preparation of many aminoacids.[1] Numerous methods describing the preparation of α-aminonitriles are reported in the literature.[2] However, most of these reactions involved lengthy reaction condition and tedious work up. Recently, Nakai[3] and Mulzer[4] have shown that TMSCN, a Lewis acid and imines to give the corresponding α-aminonitriles.

This report offers an alternative to other available methods and provides very mild, convenient, simple and fast procedure for the preparation of α-aminonitriles. Thus, α-aminonitrile **4** was prepared simply by stirring a mixture of aldehyde **1** , amine **2** and trimethylsilylcyanide **3** for 5 min. at ambient temperature in lithium perchlorate/diethylether solution (LPDE). Aromatic aldehydes as well as aliphatic aldehydes gave **4** in excellent yields.[5]

1   **2a** (R^2 = Ethyl), **2b** (R^2 = Benzyl)   **3**   **4a** (R^2 = Ethyl), **4b** (R^2 = Benzyl)

R^1	(Yield%) **4a**	(Yield%) **4b**
i-Propyl	92	90
n-Propyl	95	95
Phenyl	94	92
p-MeO-Phenyl	88	90

To study 1,3-asymmetric induction, we extended this methodology to the preparation of optically active α-aminonitriles derived from (*S*)-(-) α-methylbenzylamine and aldehydes. The reaction with both aryl and alkyl aldehydes in every case afforded mixtures of diastereoisomers with one diastereoisomer predominating. The relative stereochemistry of the products was determined by ^{1}H-NMR spectroscopy using literature methods.[6,7] For example the ^{1}H-NMR of the crude α-(1-methylbenzyl)amino valeronitrile [R^1 = *iso*-Propyl] showed two doublets, one at 2.9 ppm (J = 6.5 Hz) and the other at 3.3 ppm (J = 6.5 Hz) in ratio 80:20. Each doublet is derived from the proton attached to the carbon bearing the nitrile. On the basis of Ojima's finding the upfield (major) doublet is from the *S* chiral center of the amino nitrile proton of the molecule and the downfield (minor) doublet is from the *R* chiral center.[6] In all cases in this reaction *S*-**5** and *R*-**5** give similar enantiomeric results. In addition, similar stereochemical results were obtained by Ojima[6] and Stout[7] in their studies of TMSCN or potassium cyanide addition to chiral Schiff's bases when the bases are prepared from *S*-**5** and *R*-**5**.

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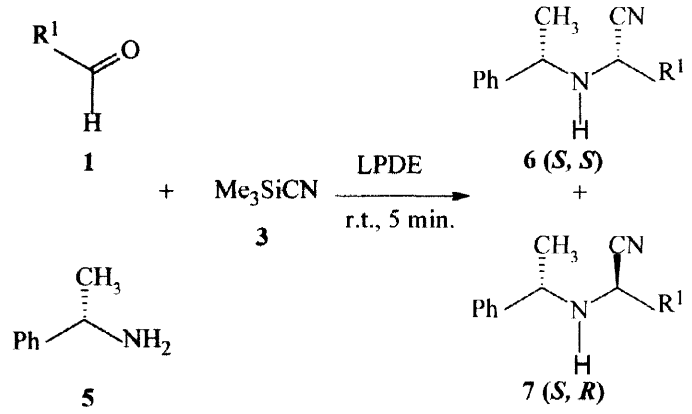

R¹	6:7	Yield %
i-Propyl	80:20	95
tert-Butyl	78:23	97
Phenyl	85:15	93
p-MeO-Phenyl	83:17	93

The diastereoselectivity achieved in our method can be explained on the basis of aza analogue of Anh-Eisenstein hypothesis.[8] According to this hypothesis nucleophilic attack on the imine should take place antiperpendicular to the α-phenyl group. There is other work on the attack of TMSCN on imines with an adjacent stereogenic center, which also been explained on the same way.[9]

In summary, we have found that 5*M* LPDE promotes the direct conversion of aldehydes into α-aminonitriles. The protocol is simple and potentially leading to versatile α-aminonitriles. This method has a few noteworthy features: 1) excellent yield can obtained for both aliphatic and aromatic aldehydes 2) great operational simplicity at ambient temperature 3) high levels of diastereoselection can be obtained in the synthesis of the α-aminonitriles using (*R*)-, (*S*)-methylbenzylamine.

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5. **A typical experimental procedure is the following:** To a mixture of aldehyde (2 mmol) in LPDE (4 ml) were added amine (2.2 mmol) at room temperature. The mixture was stirred 2 min. and TMSCN (2 mmol) was added to the same pot. The mixture was stirred for 5 min. then water was added and the product was extracted with CH_2Cl_2. The organic phase was collected, dried (Na_2SO_4) and evaporated to afford the crude product. The product purified by flash chromatography.
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