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Stereoselective Addition of Cyanide Reagents to Nitrones.

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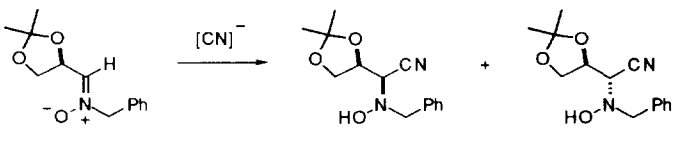
Abstract: *An exploration of the diastereoselective addition of cyanide reagents to the nitrone 1 derived from D-glyceraldehyde acetonide to afford mixtures of syn-2 and anti-2 is presented. Trimethylsilyl cyanide was found to add to the nitrone 1 with essentially complete syn-stereoselectivity in excellent yields.*

The diastereoselective synthesis of α-amino nitriles is a well-established method for the preparation of a variety of α-amino acids and it has been extensively investigated in the past years.[1] Optically active α-amino nitriles have been described to be prepared by the treatment of a carbonyl compound with a cyanide anion in the presence of either ammonium chloride or salts of amines (Strecker synthesis).[1a] However in some cases the α-amino nitriles are difficult to obtain with high yields and stereocontrol by the use of the standard Strecker conditions;[2] several modifications have been described,[3] the most used being the addition of a cyanide equivalent to a chiral imine.[1b,4] Alternative approaches consisting of the addition of cyanide to other chiral, non-racemic substrates bearing a carbon-nitrogen double bond have not been investigated.

Recently, we have demonstrated the synthetic utility of nitrones in the preparation of several nitrogen-containing enantiomerically pure compounds of interest such as α-amino aldehydes,[5] aminosugars[6] and amino acids.[7] Nitrones are readily available from aldehydes[8] and ketones[9] and they are excellent electrophilic substrates capable of reacting with a variety of nucleophiles showing a higher reactivity and stability than imines. Herein we detail our observations on the diastereoselective addition of several cyanide reagents to nitrone **1** and report the first example of α-amino nitrile synthesis by cyanide addition to a C=N system different from an imine.



1 **syn-2** **anti-2**

Scheme 1

The results of our investigation are presented in Table 1. The reaction of trimethylsilyl cyanide with **1** in dichloromethane at 0 °C (entry 1) occurred with high syn-selectivity although 2 days are needed for going to completion. The obtained O-silylated adduct can be readily transformed into α-hydroxyamino nitrile[10] **syn-2** by treatment with 4% p/v citric acid in methanol at room temperature.[11]

Table 1. Diastereoselective Addition of Cyanide Reagents to Nitrone **1**.[a]

entry	cyanide reagent	additive[b]	temperature	time	syn/anti[c]	yield (%)[d]
1	Me_3SiCN[e]	none	0 °C	48 h	**≥95 : 5**	84[f]
2	Me_3SiCN	Et_2AlCl	0 °C	4 h	≥95 : 5	68[f]
3	Et_2AlCN	Me_3SiCl[g]	0 °C	2 h	≥95 : 5	71[f]
4	Et_2AlCN	Me_3SiCl	0 °C	2 h	46 : 54	80[f]
5	Et_2AlCN	none	0 °C	2 h	**30 : 70**	90
6	Et_2AlCN[e]	none	0 °C	2 h	44 : 56	65
7	Et_2AlCN	Et_2AlCl	0 °C	2 h	44 : 56	80
8	Et_2AlCN	$ZnBr_2$	0 °C	4 h	65 : 35	86
9	Et_2AlCN	none	-60 °C	6 h	89 : 11	90
10	Et_2AlCN	Et_2AlCl	-60 °C	6 h	86 : 14	82
11	Bu_4NCN	none	-60 °C	12 h	83 : 17	86
12	Bu_4NCN	Et_2AlCl	-60 °C	12 h	74 : 26	64
13	LiCN[h]	none	-60 °C	2 h	86 : 14	82
14	LiCN[h]	Et_2AlCl	-60 °C	2 h	80 : 20	80

[a] All reactions were carried out in dichloromethane as a solvent and using 1.0 eq of cyanide reagent unless otherwise indicated. Change of the solvent did not affect to the stereoselectivity of the reaction. [b] Nitrone was precomplexed with 1.0 eq of the additive prior to the addition unless otherwise indicated. [c] Measured from the intensities of ^1H NMR signals at δ 3.60 (anti-**2**) and δ 3.79 (syn-**2**). [d] Determined on isolated mixtures of syn- and anti-adducts. [e] 5.0 eq were used. [f] The O-trimethylsilyl derivative was obtained. [g] Nitrone was added to a mixture of Et_2AlCN and trimethylchlorosilane. [h] The reaction was carried out in 1:1 THF-CH_2Cl_2 as a solvent.

Guided by our previous results on nucleophilic additions to nitrones,[12] compound **1** was precomplexed with Et_2AlCl and trimethylsilyl cyanide was then added to the reaction mixture. As evidenced by entry 2 this had no effect on the diastereoselectivity of the reaction albeit a lower chemical yield was observed. Likewise it became evident that some kind of activation took place as judged by the time of the reaction. This result prompted us to consider the possibility of the previous reaction between the aluminum reagent and trimethylsilyl cyanide to give Et_2AlCN and trimethylchlorosilane as described (equation 1).[13]

$$\left[\text{1-AlEt}_2\text{Cl} \rightleftharpoons \mathbf{1} + \text{Et}_2\text{AlCl}\right] \xrightarrow{\text{Me}_3\text{SiCN}} \mathbf{1} + \text{Et}_2\text{AlCN} + \text{Me}_3\text{SiCl} \qquad (1)$$

In fact when a solution of trimethylsilyl cyanide was treated with Et_2AlCl at room temperature for 3 h (in order to generate Et_2AlCN in the presence of trimethylchlorosilane) and nitrone **1** was added to this mixture an identical result was obtained (entry 3). By contrast when **1** was previously treated with trimethylchlorosilane and a solution of pure Et_2AlCN in dichloromethane was added to the mixture, a complete lack of stereoselectivity was observed (entry 4). We turned our attention to the use of Et_2AlCN as a cyanide equivalent.

The addition of Et_2AlCN to **1** in dichloromethane at 0 °C gave rise to a modest degree of inversion in the stereochemical course of the reaction affording α-hydroxylamino nitrile[10] anti-**2** as the major product[14] (entry 5). Increasing the stoichiometry of the cyanide reagent (entry 6) or precomplexation of **1** with Lewis acids prior to the addition (entries 7 and 8) did not afford better results. Surprisingly when the addition of Et_2AlCN was conducted at lower temperatures (-60 °C) a notably increasing in the proportion of syn-**2** was observed both in the absence and in the presence of Et_2AlCl (entries 9 and 10). We also checked the action of other cyanide reagents such as tetrabutylammonium cyanide[15] (entry 11) and lithium cyanide[16] (entry 13). In both cases syn-**2** was the major adduct. Precomplexation of **1** with Et_2AlCl had little effect on the selectivity of the reaction (entries 12 and 14).

It is possible to assume a transition state model **A** similar to that proposed by us previously[5b,7] for the addition of non-chelating cyanide reagents in the absence of Lewis acids (Figure 1). However it is difficult to reconcile the stereochemical outcome of the reaction in the presence of Et_2AlCl with our previous studies.[5b,7] The possibility of the formation *in situ* of Et_2AlCN when Et_2AlCl is present as well as the fact that Et_2AlCN can act both like a cyanide-transfer reagent and a chelating agent (leading to internal **B** and/or external **C** cyanide delivery, respectively) makes that no general trends with predictive value can be established and confirmation of the precise mechanism of the addition must await further studies.

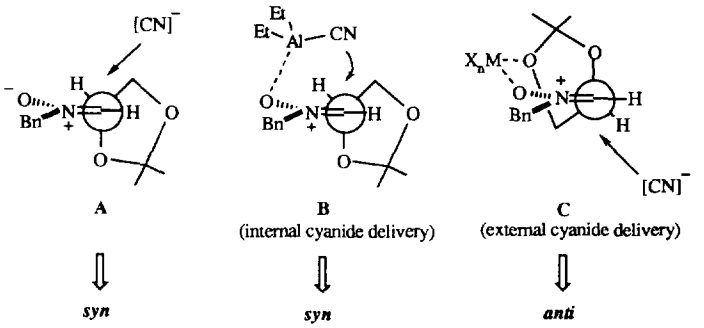


Figure 1. Transition state models for the addition of cyanide to Nitrone **1**.

The preliminary results presented in this communication represent the first evidence that cyanide nucleophiles can be added to carbon-nitrogen double bonds different from imines such as nitrones, the reaction taking place with almost complete syn selectivity when trimethylsilyl cyanide was used. Moreover the use of Et_2AlCN at 0 °C leads to anti-adducts with a synthetically useful level of selectivity. The extension of this reaction to other chiral substrates in order to understand the stereochemical outcome of the process are now under study in our laboratory. The results of these studies as well as the scope of this new reactivity and its application to Organic Synthesis will be reported in due time.

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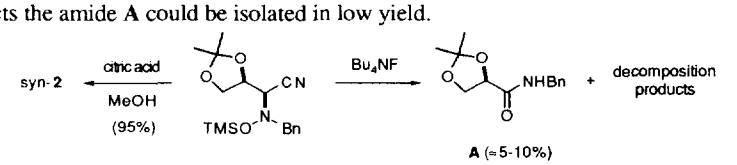
10. syn-**2**: colourless needles; $[\alpha]_D$ = -34.8° (c 0.87, $CHCl_3$); mp 116 °C; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.32 (s, 3H), 3.75 (d, 1H, J = 7.1 Hz), 3.91 (d, 1H, J = 12.5 Hz), 4.02 (dd, 1H, J = 4.6, 9.5 Hz), 4.12 (dd, 1H, J = 6.1, 9.5 Hz), 4.19 (d, 1H, J = 12.5), 4.42 (ddd, 1H, J = 4.6, 6.1, 7.1 Hz), 6.26 (bs, 1H, ex. D_2O), 7.33-7.36 (m, 5H). anti-**2**: transparent blocks; $[\alpha]_D$ = +8.6° (c 0.80, $CHCl_3$); mp 132 °C; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.43 (s, 3H), 3.58 (d, 1H, J =7.9 Hz), 3.84 (d, 1H, J = 12.6 Hz), 3.94 (dd, 1H, J = 4.0, 9.2 Hz), 4.04 (dd, 1H, J = 5.9, 9.2 Hz), 4.14 (d, 1H, J = 12.6 Hz), 4.42 (ddd, 1H, J = 4.0, 5.9, 7.9 Hz), 5.39 (bs, 1H, ex. D_2O), 7.33 (bs, 5H).
11. Attempts of desilylation with tetrabutylammonium fluoride only lead to decomposition products. Among these products the amide **A** could be isolated in low yield.



12. It has been well-demonstrated by us that nucleophilic additions of metalated heterocycles to α-alkoxy nitrones can be stereocontrolled by carrying out the reaction in the absence or in the presence of Lewis acids (e.g. Et_2AlCl) to give syn- or anti- adducts, respectively (see refs. 5-7). On the other hand the previous treatment of **1** with Me_3SiCl leads to syn- adducts (see: Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F.L.; Merino, P.; Tejero, T. *Chemistry: A European Journal* **1995**, in press).
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14. The stereochemical assignement of compounds **2** was unequivocally established by a X-ray crystallographic analysis of anti-**2** (Merino, P.; Merchan, F.L.; Tejero, T. *unpublished results*).
15. Bu_4NCN was prepared by treatuing a solution of trimethylsilyl cyanide in dichloromethane with anhydrous tetrabutylammonium fluoride.
16. LiCN was prepared by treating a solution of trimethylsilyl cyanide in dichloromethane with a 1.6 M solution of butyllithium in hexanes.

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