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Highly Diastereoselective Addition of Trimethylsilyl Cyanide to Chiral Hydrazones in the Presence of Et₂AlCl

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Abstract. Chiral hydrazones, synthesized from (S)-1-amino-2-methoxymethylindoline and aliphatic aldehydes, reacted with trimethylsilyl cyanide in the presence of diethylaluminium chloride in CH₂Cl₂ at -78 °C to give chiral α -hydrazinonitriles with high diastereoselectivity (up to 96% de). Copyright © 1996 Elsevier Science Ltd

The asymmetric synthesis of α -aminonitriles constitutes an important method for the synthesis of chiral α -amino acids. Diastereoselective Strecker synthesis involving the additions of cyanide to chiral imines obtained from aldehydes and chiral auxiliaries such as α -methylbenzyl amine¹. (4*S*, 5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane². 1-amino-tetra-O-pivaloyl- β -D-galactopyranose³, and α -phenylglycinol⁴ has been reported to afford α -aminonitriles in useful levels of diastereoselectivity (up to 86% de³) and crystallization often provided for the pure diastereomers. Recently, asymmetric Strecker synthesis using enantiopure sulfinimines has been reported ⁵ to give optical induction of up to 86% de before isolation. But, there has never been reported on diastereoselective addition of cyanide to chiral hydrazones.

In this paper, we report that diastereoselective addition of trimethylsilyl cyanide (TMSCN) to (S)-1amino-2-methoxymethylindoline (SAMI) hydrazones in the presence of diethylaluminium chloride afforded the corresponding chiral α -hydrazinonitriles in high chemical yields and optical yields (up to 96% de) without crystallization or isolation. Recently, we reported that SAMI is an excellent chiral auxiliary in the diastereoselective addition of organolithium reagents to SAMI hydrazones.⁶

Chiral hydrazone la obtained from pivalaldehyde and SAMI was used as a substrate in the addition of TMSCN in the presence of various Lewis acids in order to optimize the reaction conditions. The results obtained are summarized in Table 1. In the reaction of 1a with TMSCN in the presence of Lewis acid such as SnCl₄, BF₃OEt₂, or ZnCl₂, most of starting material remained at -78 °C in THF or CH₂Cl₂ after As the reaction temperatures were raised up to 0 °C, the reactions proceeded completely stirring for 10 h. but optical yields were not satisfactory (run 1-4; 50-68% de). Surprisingly, the reaction proceeded smoothly at -78 $^{\circ}$ C in CH₂Cl₂ for 9 h in the presence of EtAlCl₂ or Et₂AlCl to afford 4a with high diastereoselectivity (run 5; 92% de with EtAlCl₂, run 6; 94% de with Et₂AlCl). Diethylaluminium chloride resulted in the higher selectivity. Another substrate 2 which has longer side chain (MOM) reacted under same reaction conditions to give similar result (run 7; 92% de), while 3 containing bulky TBDMS group afforded 5 in less optical yields (run 8; 82% de with EtAlCl₂, run 9; 88% de with Et₂AlCl) than 1a. The 1b containing isopropyl moiety (R1) resulted in the highest diastereoselectivity (96% de). When substrate le containing tosylate side chain reacted, 4e was also obtained with high diastereoselectivity (90% de) where tosylate moiety was inert in the reaction. Consequently, the best results were obtained in the reactions at -78 °C in CH₂Cl₂ in the The ratios of diastereomers were determined by 1H NMR and/or HPLC analysis presence of Et₂AlCl. (CHIRAL CELL OD, 25cm x 0.46cm) of crude reaction mixtures.

$H_{1-3 R^{1}}^{N} \rightarrow H$									
_Run	Reactan	ts R	R ¹	Lewis Acid	Solvent	Temp.(°C)	Products	Yield ^b (%	6) de ^c (%)
1	1a	CH ₃	t-Bu	SnCl₄	THF	-78 - 0	4a	90	68
2	1a	CH ₃	t-Bu	BF ₃ OÉt ₂	CH_2Cl_2	-78 - 0	4a	91	52
3	1a	CH ₃	t-Bu	BF ₃ OEt ₂	T ĤF	-78 - 0	4a	75	50
4	1a	CH ₃	t-Bu	$ZnCl_2$	CH ₂ Cl ₂	-78 - 0	4a	92	52
5	1a	CH ₃	t-Bu	$EtAlC\overline{l}_{2}$	CH_2Cl_2	-78	4a	84	92
6	1a	CH ₃	t-Bu	Et ₂ AlCĪ	CH ₂ Cl ₂	-78	4a	82	94
7	2	CH ₂ OCH ₃	t-Bu	Et ₂ AlCl	CH_2Cl_2	-78	5	73	92
8	3	SiMe ₂ t-Bu	t-Bu	EtAlCl ₂	CH_2Cl_2	-78	6	67	82
9	3	SiMe ₂ t-Bu	t-Bu	Et ₂ AlCl	CH_2Cl_2	-78	6	70	88
10	1b	CH ₃	i-Pr	Et ₂ AlCl	CH_2Cl_2	-78	4b	91	96
11	1c	CH ₃	n-Bu	Et ₂ AlCl	CH_2Cl_2	-78	4c	80	90
12	1d	CH_3	Et	Et ₂ AlCi	CH_2Cl_2	-78	4d	87	90
13	1e	CH ₃ (C	$(H_2)_4 OT_2$	s Et ₂ AICI	CH_2Cl_2	-78	4e	85	90

Table 1. Diastereoselective Additions of TMSCN to Chiral Hydrazones 1-3 in the presence of Lewis Acids^a.

a. All reactions were carried out with 3 eq. of TMSCN and 2 eq. of Lewis acid for 9 hours. b. Isolated Yield.

c. Determined by 'H NMR and/or HPLC analysis (CHIRAL CELL OD).

To remove the chiral auxiliary and determine the absolute configuration of 4, hydrogenation was carried out under the usual conditions using Pd/C catalyst in DME including HCl.⁶ Unexpectedly, dehydrogenation occurred instead of N-N bond cleavage to give a hydrazonoyl cyanide.⁷ Hydrogenolysis of 4d using Pd(OH)₂/C catalyst in CH₃CO₂H under H₂ produced the chiral vicinal diamine, which was treated with salicylaldehyde in methanol to provide the disalicylidene diamine 5 (α_D -201 (c 0.9, CHCl₃), 51% from 4d), whose configuration was confirmed to be *R* form by comparison of its authentic compound (*R*)-5 (α_D -223 (c 0.72, CHCl₃)) which was synthesized through several steps from (*R*)-(-)-2-amino-1-butanol by the known methods.⁸



Further studies on the mechanism, scope, and cleavage of N-N bond of 4 are in progress. Acknowledgement : This work was supported by CBM from KOSEF.

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- The (R)-5 was prepared in total 35% yield from (R)-(-)-2-amino-1-butanol: (a) CbzCl, NEt₃, CH₂Cl₂ (b) MsCl, NEt₃, CH₂Cl₂, 0 °C (c) NaN₃, DMF, 100 °C (d) H₂, Pd(OH)₂, CH₃OH (e) salicylaldehyde, CH₃OH.

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