Pergamon

Tetrahedron Letters, Vol. 37, No. 43, pp. 7795-7796, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 \$15.00 + 0.00

PII: S0040-4039(96)01780-7

Highly Diastereoselective Addition of Trimethylsilyl Cyanide to Chiral Hydrazones in the Presence of Et_2AlCl

Jun Young Choi and Yong Hae Kim*

Department of Chemistry, Korea Advanced Institute of Science and Technology, 373-1,
Kusong Dong, Yusong Gu, Taejon 305-701, Korea

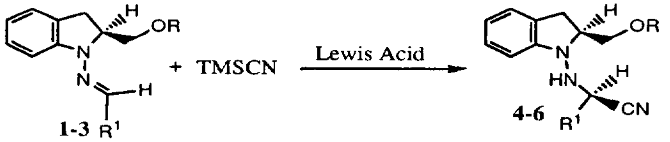
Abstract: Chiral hydrazones, synthesized from (*S*)-1-amino-2-methoxymethylindoline and aliphatic aldehydes, reacted with trimethylsilyl cyanide in the presence of diethylaluminium chloride in CH_2Cl_2 at -78 °C to give chiral α-hydrazinonitriles with high diastereoselectivity (up to 96% de).
Copyright © 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 amine[1], (4*S*, 5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane[2], 1-amino-tetra-O-pivaloyl-β-D-galactopyranose[3], and α-phenylglycinol[4] has been reported to afford α-aminonitriles in useful levels of diastereoselectivity (up to 86% de[3]) 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*)-1-amino-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 **1a** 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 $SnCl_4$, BF_3OEt_2, or $ZnCl_2$, most of starting material remained at -78 °C in THF or CH_2Cl_2 after stirring for 10 h. As the reaction temperatures were raised up to 0 °C, the reactions proceeded completely but optical yields were not satisfactory (run 1-4; 50-68% de). Surprisingly, the reaction proceeded smoothly at -78 °C in CH_2Cl_2 for 9 h in the presence of $EtAlCl_2$ or Et_2AlCl to afford **4a** with high diastereoselectivity (run 5; 92% de with $EtAlCl_2$, run 6; 94% de with Et_2AlCl). 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 $EtAlCl_2$, run 9; 88% de with Et_2AlCl) than **1a**. The **1b** containing isopropyl moiety (R^1) resulted in the highest diastereoselectivity (96% de). When substrate **1e** 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 CH_2Cl_2 in the presence of Et_2AlCl. The ratios of diastereomers were determined by ^1H NMR and/or HPLC analysis (CHIRAL CELL OD, 25cm x 0.46cm) of crude reaction mixtures.

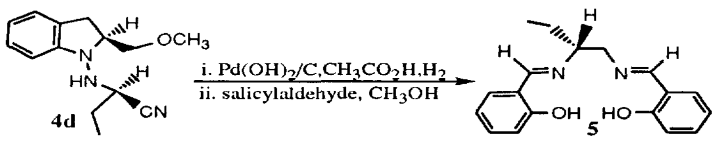
Table 1. Diastereoselective Additions of TMSCN to Chiral Hydrazones 1-3 in the presence of Lewis Acids[a].



Run	Reactants	R	R^1	Lewis Acid	Solvent	Temp.(°C)	Products	Yield[b](%)	de[c](%)
1	**1a**	CH_3	t-Bu	$SnCl_4$	THF	-78 - 0	**4a**	90	68
2	**1a**	CH_3	t-Bu	BF_3OEt_2	CH_2Cl_2	-78 - 0	**4a**	91	52
3	**1a**	CH_3	t-Bu	BF_3OEt_2	THF	-78 - 0	**4a**	75	50
4	**1a**	CH_3	t-Bu	$ZnCl_2$	CH_2Cl_2	-78 - 0	**4a**	92	52
5	**1a**	CH_3	t-Bu	$EtAlCl_2$	CH_2Cl_2	-78	**4a**	84	92
6	**1a**	CH_3	t-Bu	Et_2AlCl	CH_2Cl_2	-78	**4a**	82	94
7	**2**	CH_2OCH_3	t-Bu	Et_2AlCl	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_2AlCl	CH_2Cl_2	-78	**6**	70	88
10	**1b**	CH_3	i-Pr	Et_2AlCl	CH_2Cl_2	-78	**4b**	91	96
11	**1c**	CH_3	n-Bu	Et_2AlCl	CH_2Cl_2	-78	**4c**	80	90
12	**1d**	CH_3	Et	Et_2AlCl	CH_2Cl_2	-78	**4d**	87	90
13	**1e**	CH_3	$(CH_2)_4OTs$	Et_2AlCl	CH_2Cl_2	-78	**4e**	85	90

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 ^1H 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 CH_3CO_2H under H_2 produced the chiral vicinal diamine, which was treated with salicylaldehyde in methanol to provide the disalicylidene diamine **5** (α_D -201 (c 0.9, $CHCl_3$), 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, $CHCl_3$)) 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.

References and Notes

1. (a) Harada, K. *Nature* (London) **1963**, *200*, 1201. (b) Harada, K.; Okawara, T. *J. Org. Chem.* **1973**, *38*, 707-710. (c) Ojima, T.;Inaba, S. *Chem. Lett.* , **1975**, 737-740.
2. (a) Weinges, K.; Brune, G.; Droste, H. *Liebigs Ann. Chem.,1980*, 212-218. (b) Weinges, K.; Brachmann, H.; Stahnecker, P.; Rodewald, H. *ibid*, **1985**, 566-578.
3. (a) Kunz, H.; Sager, W. *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*, 557-559. (b) Kunz, H.; Sager, W.; Pfrengle, W.; Schanzenbach, D. *Tetrahedron Lett.* **1988**, *29*, 4397-4400.
4. Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* ,**1995**, *51*, 9179-9190.
5. Davis, T. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y. *J. Org. Chem*, **1996**, *61*, 440-441.
6. Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.*, **1996**, *37*, 5543-5546.
7. The paper on the novel dehydrogenation and its application will be published.
8. The (*R*)-**5** was prepared in total 35% yield from (*R*)-(-)-2-amino-1-butanol: (a) CbzCl, NEt_3,CH_2Cl_2 (b) MsCl, NEt_3, CH_2Cl_2, 0 °C (c) NaN_3, DMF, 100 °C (d) H_2, $Pd(OH)_2$, CH_3OH (e) salicylaldehyde, CH_3OH.

(*Received in Japan* 6 *August* 1996; *revised* 2 *September* 1996; *accepted* 10 *September* 1996)