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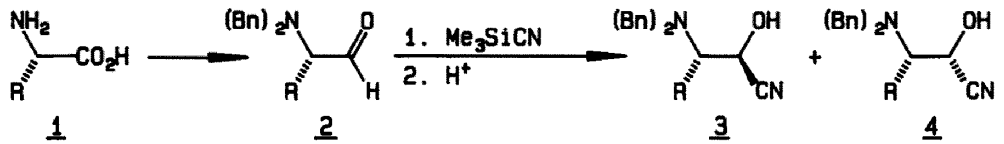
STEREOSELECTIVE CYANOHYDRIN-FORMING REACTIONS OF CHIRAL α-AMINO ALDEHYDES

M.T. Reetz*, M.W. Drewes, K. Harms and W. Reif

Fachbereich Chemie der Universität, Hans-Meerwein-Strasse, 3550 Marburg, FRG

Summary: The Lewis acid mediated cyanohydrin-forming addition of Me_3SiCN to optically active α-dibenzylamino aldehydes 2 occurs stereoselectively. Chelation controlled adducts 3 result if $MgBr_2$ or $TiCl_4$ is used, whereas the diastereomers 4 are obtained upon employing BF_3, $ZnBr_2$ or $SnCl_4$.

We have previously shown that N,N-dibenzylamino aldehydes 2 undergo stereoselective Grignard-type and aldol additions.[1] Since the aldehydes are readily synthesized from the corresponding acids 1, such C-C bond forming reactions amplify the importance of the "chiral pool" of amino acids.[2] We now report that cyanohydrin-forming reactions using Me_3SiCN in the presence of equivalent amounts of Lewis acids also occur stereoselectively.[3]



It is shown in Table 1 that the Lewis acids BF_3, $ZnBr_2$ or $SnCl_4$ lead to the non-chelation controlled adducts[4] 4 preferentially, whereas $TiCl_4$ or $MgBr_2$ result in chelation control. In some cases the O-silyl-cyanohydrins are the actual primary products (e.g., when $ZnBr_2$ or $MgBr_2$ are used), but the crude products can be worked up with methanolic citric acid so as to deliver the final desilylated compounds 3/4. The products are enantiomerically pure, which means that no racemization of 2 occurs during C-C bond formation.[5]

The configurational assignment of 3/4 is based primarily on an X-ray structural analysis of adduct 4b (R=CH_2Ph), which is formed in the $SnCl_4$, BF_3 or $ZnBr_2$ mediated addition of Me_3SiCN to the aldehyde 2b derived from L-phenylalanine 1b (Fig. 1).[6] Accordingly, this diastereomer is clearly the non-chelation controlled adduct corresponding to the relative configuration shown in 4. This means that the $TiCl_4$ and $MgBr_2$ promoted reactions afford the

diastereomer having the opposite relative configuration 3b. The configurational assignments of the other adducts were made on the basis of analogy. The ^{1}H- and ^{13}C-NMR data[7] do not allow for general rules regarding the configurational assignments, in contrast to the previously reported Grignard adducts[1]. However, the chelation controlled adducts 3 move a little faster on tlc plates than do 4, a phenomenon that also pertains in the case of Grignard and aldol adducts.[1]

Table 1. Stereoselective Me_3SiCN Additions to Amino Aldehydes 2

Aldehyde	Lewis acid	Temp./Time (°C/h)	Yield (%)	ratio 3:4
2a (R=CH_3)	$ZnBr_2$	-20/ 3	74	5:95
2a (R=CH_3)	$TiCl_4$[a)]	-60/16	61	82:18
2b (R=CH_2Ph)	$BF_3 \cdot OEt_2$	-10/10	74	5:95
2b (R=CH_2Ph)	$ZnBr_2$	-20/ 3	79	5:95
2b (R=CH_2Ph)	$SnCl_4$	-78/ 3	67	13:87
2b (R=CH_2Ph)	$TiCl_4$[a)]	-60/16	58	78:22
2b (R=CH_2Ph)	$MgBr_2$	-20/ 3	76	78:22
2c (R=CH_2CHMe_2)	$ZnBr_2$	-20/ 3	78	5:95
2c (R=CH_2CHMe_2)	$TiCl_4$[a)]	-60/16	63	88:12
2d (R=$CHMe_2$)	$ZnBr_2$	-20/ 3	81	5:95
2d (R=$CHMe_2$)	$SnCl_4$	-78/ 3	67	5:95
2d (R=$CHMe_2$)	$TiCl_4$[a)]	-60/16	63	84:16
2d (R=$CHMe_2$)	$MgBr_2$	-20/ 3	75	82:18

a) Two equivalents of Me_3SiCN used. Solvent in all cases: CH_2Cl_2

Non-chelation control in reactions of 2 was previously noted to be in line with the Felkin-Anh model,[1] whereas the chelation controlled adducts are likely to be formed via intermediates 5. Since $SnCl_4$ mediated allylsilane additions to 2 occur with chelation control,[1] the stereochemical outcome of the present $SnCl_4$ induced addition of Me_3SiCN is surprising. Preliminary NMR experiments of 1:1 mixtures of 2b (R=CH_2Ph) and $SnCl_4$ show the presence of at least three species in the temperature range of -78°C to 0°C. Since dynamic effects appear to be involved (generally broad lines), they could not be identified, but open-chain Lewis acid adducts are likely to be involved. Similar results were obtained when using $TiCl_4$. Apparently, the Curtin-Hammett principle pertains in these systems, making mechanistic studies difficult. The reactions in the case of $MgBr_2$ are heterogeneous, a 1:1 mixture (slurry) showing no signs of an adduct (merely non-complexed 2). In the case of $TiCl_4$ two equivalents of Me_3SiCN must be used. It is likely that the first equivalent undergoes an exchange reaction with $TiCl_4$ to form Cl_3TiCN adducts which then react with the second equivalent of Me_3SiCN.[8]

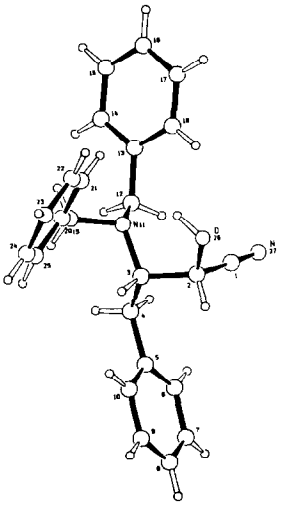
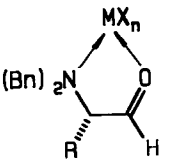


Fig. 1 SCHAKAL drawing of 4b



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M = metal
X = halogen

Irrespective of the precise mechanisms, the present methodologies are of synthetic interest since cyanohydrins are useful vehicles for further transformations. For example, the rational synthesis of a number of low molecular weight peptides such as amastatin, epiamastatin, bestatin and epibestatin, all of which contain β-amino alcohol units,[9] is now possible. Previous attempts to convert N-protected α-amino aldehydes into the corresponding cyanohydrins resulted in essentially stereorandom formation of diastereomers.[9]

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REFERENCES AND NOTES:

1) Reetz, M.T., Drewes, M.W. and Schmitz, A., Angew.Chem. 99 (1987) 1186; Angew.Chem.Int.Ed.Engl. 26 (1987) 1141.

2) Martens, J., Top.Curr.Chem. 125 (1984) 165; Coppola, G.M. and Schuster, H.F., Asymmetric Synthesis, John Wiley, New York 1987.

3) General procedure: The mixture of an aldehyde 2 (1.06 mmol), trimethylsilylcyanide (121 mg; 1.21 mmol) and $ZnBr_2$ (272 mg; 1.21 mmol) in dry CH_2Cl_2 (10 ml) is stirred at -20°C for 4 h. The reaction mixture is poured onto 5 ml of H_2O and the organic phase extracted with ether. The combined organic phases is washed with brine, dried over $MgSO_4$ and concentrated, yielding the O-silylated form of 4. If the free hydroxy form 4 is desired, workup is performed with 10% methanolic citric acid (5 ml) and the product chromatographed on silica gel (pet-ether/ether in a ratio of 100:1). In the case of chelation control, the equivalent amounts of aldehyde 2 and $TiCl_4$ are mixed in 10 ml of CH_2Cl_2 at -78°C and two equivalents of Me_3SiCN added. After stirring at -60°C for 16 h, the mixture is poured onto 10% methanolic citric acid and worked up as above.

4) Review of chelation and non-chelation controlled additions to chiral alkoxy carbonyl compounds: Reetz, M.T., Angew.Chem. 96 (1984) 542; Angew. Chem.Int.Ed.Engl. 23 (1984) 556.

5) This was checked by applying the Mosher method in the optically active and racemic series; cf. Dale, J.A., Dull, D.L. and Mosher, H.S., J.Org.Chem. 34 (1969) 2543.

6) Crystal data (K. Harms): $C_{24}H_{24}N_2O$, M=356.47, triclinic, P -1, a=8.225(2), b=10.598(2), c=12.754(2) Å, α=96.30(1), β=105.52(1), γ106.17(1)°, V=1007.6 $Å^3$, Z=2, D_C=1.17gcm^{-3}, μ(CuKα)=5.3cm^{-1}. 2660 independent observed reflections [I>4σ(I), Θ_{max}=120°] were measured on an Enraf-Nonius CAD4 diffractometer with monochromated CuKα-radiation. Structure solution with direct methods (SHELXS-86, G.M. Sheldrick, Goettingen, FRG, 1986), refinement with the Enraf-Nonius SDP-system, all non hydrogen atoms anisotropically, hydrogens with fixed isotropic temperature factors, with the exception of the hydroxyl hydrogen on idealized positions using a riding model, to R=0.053, R_w=0.062 [$w^{-1}=\sigma^2(F)$]. Further details of the crystal structure are available from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England. Requests should be accompanied by a full literature citation for this communication.

7) NMR data ($CDCl_3$) for 3a (δ/ppm): ^{1}H-NMR (300 MHz): 1.17 (d,3H,J=7.4Hz), 3.16 (m,1H), 3.36 and 4.01 (AB system, 4H, J_{AB}=13.2Hz), 4.11 (d,1H,J=10.0Hz), 7.28 (m, 10H); ^{13}C-NMR (75 MHz): 8.65, 53.2, 57.06, 62.05, 118.85, 127.53-137.56 (aromatics). Date for 4a: ^{1}H-NMR (300 MHz): 1.27 (d,3H,J=6.9Hz), 3.12 (m,1H), 3.36 and 3.97 (AB system, 4H, J_{AB}=13.3Hz), 4.16 (d,1H,J=6.4Hz), 7.29 (m,10H); ^{13}C-NMR (75 MHz): 9.19, 54.29, 54.67, 62.36, 119.40, 127.71-138.03 (aromatics).

8) In the case of $TiCl_4$ mediated reactions of chiral α-alkoxy aldehydes, two equivalents of Me_3SiCN are also necessary: Reetz, M.T., Kesseler, K. and Jung, A., Angew.Chem. 97 (1985) 989; Angew.Chem.Int.Ed.Engl. 24 (1985) 989.

9) See for example: Rich, D.H., Moon, B.J. and Boparai, A.S., J.Org.Chem. 45 (1980), 2288; Nishizawa, R. and Saino, T., J.Med.Chem. 20 (1977) 510.

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