Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8479–8481

TETRAHEDRON LETTERS

Asymmetric Strecker synthesis by addition of trimethylsilyl cyanide to aldehyde SAMP-hydrazones

Dieter Enders* and Michael Moser

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor Pirlet-Str. 1, 52074 Aachen, Germany

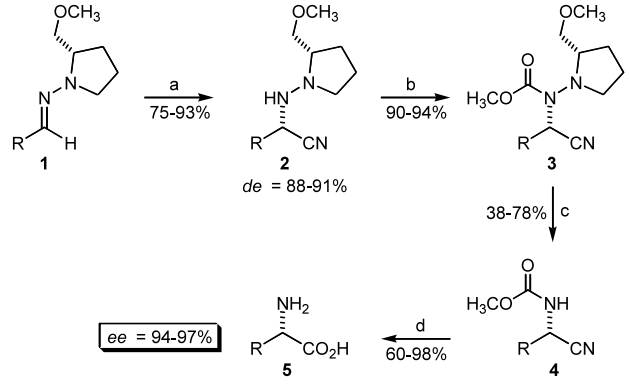
Received 24 June 2003; revised 12 September 2003; accepted 12 September 2003

Abstract—The asymmetric 1,2-addition of trimethylsilyl cyanide to aldehyde SAMP-hydrazones in the presence of titanium tetrachloride and diethylether in dichloromethane at −100°C up to room temperature, removal of the chiral auxiliary and acid hydrolysis affords α-amino acids in high enantiomeric excesses (*ee* = 94–97%).

Efficient asymmetric syntheses of naturally occurring and nonproteinogenic α-amino acids are of considerable interest because of their importance in biological systems and their usefulness as chiral building blocks in organic synthesis.[1] Since Strecker published his report[2] on the three component reaction in 1850 to synthesize α-amino nitriles there have been strong efforts recently to perform this reaction in an enantioselective way. Among the stoichiometric approaches the addition of cyanide to imines or hydrazones using chiral auxiliaries such as phenylethylamine,[3] (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane,[4] α-phenylglycinol,[5] 1-amino-tetra-*O*-pivaloyl-β-D-galacto-pyranose,[6] sulfinates[7] and (*S*)-1-amino-2-methoxymethyl-indoline (SAMI)[8] has already been investigated. However, in the case of using enantiopure hydrazones as starting material in the Strecker synthesis the cleavage of the N–N bond of the created α-hydrazino nitriles to obtain α-amino nitriles[9] was unsuccessful so far.

In this paper we report the diastereoselective addition of trimethylsilyl cyanide (TMSCN) to (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP) aldehyde hydrazones in the presence of titanium tetrachloride and diethylether to obtain α-hydrazino nitriles in high yields and diastereo-selectivities. The N–N bond of the α-hydrazino nitriles was cleaved with an oxidative method and the resulting α-amino nitriles were then converted into α-amino acids by acidic hydrolysis.

As is depicted in Scheme 1, the SAMP-hydrazones **1** were synthesized from the corresponding aldehydes and SAMP by condensation.[10] Their reaction with TMSCN in the presence of titanium tetrachloride as Lewis acid to activate the C=N bond proceeded at −100°C up to room temperature for 12 h in dichloromethane. The strong influence of the solvent used in cyano additions to the C=N double bond has already been described by Kunz et al.[6] Also under our conditions it was found that the diastereofacial selectivity in the Strecker syn-



Scheme 1. *Reagents and conditions*: (a) $TiCl_4$ (2 equiv.), TMSCN (3 equiv.), diethylether (4.2 equiv.), CH_2Cl_2, −100°C to rt, 12 h; (b) MocCl (10 equiv.), K_2CO_3 (20 equiv.), CH_2Cl_2, reflux, 7 h; (c) MMPP (9 equiv.), methanol, rt, 1 week; (d) 6 M HCl, H_2O, reflux, 7 h.

Keywords: asymmetric synthesis; α-amino acids; α-amino nitriles; hydrazones; 1,2-addition.

* Corresponding author. Tel.: +49-241-8094676; fax: +49-241-8092127; e-mail: enders@rwth-aachen.de

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.098

Table 1. Enantioselective synthesis of α-amino acids **5**

2–5	R	Yield **2** (%)[a]	*de* **2** (%)[b]	Yield **3** (%)[a]	Yield **4** (%)[a]	Yield **5** (%)[a]	*ee* **5** (%)[c]
a	Et	85	91	93	78	60	97
b	*n*-Pr	90	88	94	74	60	95
c	*i*-Pr	75	90	91	38	85	96
d	*i*-Bu	91	90	90	50	81	94
e	Bn	93	90	92	59	98	96

[a] Determined after column chromatography.
[b] Determined by ^{13}C NMR.
[c] Determined by Mosher amides.

thesis can be reversed by changing the solvent from dichloromethane to diethylether.

Interestingly, the diastereoselectivity of the reaction in dichloromethane increases from 60% up to 91% *de* in the presence of a small amount of diethylether. Under these conditions the (*S*,*S*)-diastereomers of the α-hydrazino nitriles **2** are formed in excess. The *de* values could be improved by column chromatography (Table 1).

To remove the chiral auxiliary reductive methods are useless because of the presence of the cyano group. Therefore, we decided to use magnesium monoperoxy phthalate (MMPP) as an oxidative cleavage reagent.[11] It is necessary to activate the N–N bond by adding methoxycarbonyl chloride (MocCl) to the hydrazines (*S*,*S*)-**2**. Thus, the protected α-hydrazino nitriles (*S*,*S*)-**3** were obtained by treatment of the hydrazines (*S*,*S*)-**2** with 10.0 equiv. MocCl and 20 equiv. potassium carbonate in dichloromethane for 7 h under reflux. The formation of the protected α-amino nitriles (*S*)-**4** under oxidative N–N bond cleavage was achieved by treatment of the protected α-hydrazino nitriles (*S*,*S*)-**3** with 9.0 equiv. MMPP for 1 week in methanol. The products (*S*)-**4** were hydrolyzed with concurrent removal of the Moc protecting group with 6 M HCl under reflux for 7 h. The enantiomeric excesses of the α-amino acids (*S*)-**5** were detected via the (*R*)-(+)-MTPA amides as described by Mosher (Table 1).[12]

In summary, the asymmetric Strecker synthesis of α-amino acids (*S*)-**5** was achieved in overall yields of 22–50% for the four steps and high enantiomeric excesses (*ee* = 94–97%) employing aldehyde SAMP-hydrazones as electrophiles. Key to the success was the first N–N bond cleavage of the intermediate α-hydrazino nitriles to remove the chiral auxiliary.[13–15]

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG and Bayer AG for the donation of chemicals.

References

1. (a) Barrett, G. C. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985; (b) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Exeter, 1989; (c) Duthaler, O. R. *Tetrahedron* **1994**, *50*, 1539.
2. Strecker, A. *Liebigs. Ann. Chem.* **1850**, *75*, 27.
3. (a) Harada, K. *Nature (London)* **1963**, *200*, 1201; (b) Harada, K.; Fox, S. W. *Naturwissenschaften* **1964**, *51*, 106; (c) Patel, M. S.; Worsley, M. *Can. J. Chem.* **1970**, *48*, 1881; (d) Harada, K.; Okawara, T. *J. Org. Chem.* **1973**, *38*, 707; (e) Ojima, I.; Inaba, S. *Chem. Lett.* **1975**, 737; (f) Weinges, K.; Gries, K.; Stemmle, B.; Schrank, W. *Chem. Ber.* **1977**, *110*, 2098.
4. (a) Weinges, K.; Brune, G.; Droste, H. *Liebigs Ann. Chem.* **1980**, 212; (b) Weinges, K.; Brachmann, H.; Stahnecker, P.; Rodewald, H.; Nixdorf, M.; Irngartinger, H. *Liebigs Ann. Chem.* **1985**, 566.
5. Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179.
6. (a) Kunz, H.; Sager, W. *Angew. Chem.* **1987**, *99*, 595; *Angew. Chem., Int. Ed.* **1987**, *26*, 557; (b) Kunz, H.; Sager, W.; Pfrengle, W.; Schanzenbach, D. *Tetrahedron Lett.* **1988**, *29*, 4397; (c) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651.
7. (a) Davis, F. A.; Reddy, R. E.; Portonovo, P. S. *Tetrahedron Lett.* **1994**, *35*, 9351; (b) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y. *J. Org. Chem.* **1996**, *61*, 440.
8. Choi, J. Y.; Kim, Y. H. *Tetrahedron Lett.* **1996**, *37*, 7795.
9. For a review see: Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.
10. (a) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933; (b) Review: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.
11. (a) Fernández, R.; Ferrete, A.; Lassaletta, J. M., Llera, J. M.; Monge, A. *Angew. Chem.* **2000**, *112*, 3015; *Angew. Chem., Int. Ed.* **2000**, *39*, 2893; (b) Enders, D.; Braig, V.; Raabe, G. *Can. J. Chem.* **2001**, *79*, 1528.
12. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
13. General procedure for the preparation of compounds (*S*,*S*)-**2** and (*S*)-**4**.
Synthesis of α-hydrazino nitriles (*S*,*S*)-**2**: 2.0 equiv. 1.0 M $TiCl_4$ solution in CH_2Cl_2 were treated with 1.0 equiv. hydrazone (*S*)-**1** in abs. CH_2Cl_2 (5 mL/mmol (*S*,*S*)-**2**) at −78°C and stirred for 15 min. 4.2 equiv. diethylether were added and after 15 min the mixture was cooled to −100°C. 1.5 equiv. TMSCN were added rapidly and the solution was stirred overnight while it was allowed to warm up to room temperature. Upon aqueous work up (aq. NH_4F, CH_2Cl_2, $MgSO_4$) the α-hydrazino nitriles (*S*,*S*)-**2** were purified by column chromatography (SiO_2, *n*-pentane/diethylether).

Synthesis of Moc-protected α-amino nitriles (*S*)-**4**: Moc-protected α-hydrazino nitriles (*S*,*S*)-**3** were dissolved in methanol (20 mL/mmol (*S*,*S*)-**3**). 3.0 equiv. MMPP were added and the mixture was stirred 1 week at room temperature while it was added every day 1.0 equiv. MMPP. Upon aqueous work up (aq. $NaHCO_3$, CH_2Cl_2, $MgSO_4$) the α-amino nitriles (*S*)-**4** were purified by column chromatography (SiO_2, *n*-pentane/diethylether).

14. Selected analytical and spectroscopic data of compounds (*S*,*S*)-**2c** and (*S*)-**4c**.
(*S*,*S*)-**2c**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.07$ (d, $J = 6.9$ Hz, 6H, $CH(CH_3)_2$), 1.51 (m, 1H, $NCHCHHCH_2$), 1.72–2.03 (m, 4H, $NCHCHHCH_2$, $NCHCH_2CH_2$, $CH(CH_3)_2$), 2.36 (q, $J = 8.9$ Hz, 1H, NCHH), 2.74 (m, 1H, $NCHCH_2CH_2$), 3.32–3.62 (m, 5H, CH_2O, NCHH, CHCN, NH), 3.38 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 17.8$, 19.5, 20.9, 25.7, 29.8, 56.5, 58.8, 58.8, 64.6, 75.6, 119.9; MS (EI): $m/z = 211$, 167, 166, 164, 139, 130, 129, 97, 85, 84, 71, 70, 61, 55, 82, 45; IR (film): 3581, 3298, 2965, 2876, 2831, 2391, 2243, 1640, 1466, 1390, 1372, 1355, 1302, 1254, 1193, 1099, 1001, 971, 917, 879, 818, 632, 589, 527 cm^{-1}; HRMS: $C_{11}H_{21}N_3O$: calcd 211.1685; found 211.1684.
(*S*)-**4c**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.08/1.11$ (2d, $J = 6.9/6.9$ Hz, 6H, $CH(CH_3)_2$), 2.06 (m, 1H, $CH(CH_3)_2$), 3.73 (s, 3H, OCH_3), 4.49 (m, 1H, CHCN), 5.74 (d, $J = 7.4$ Hz, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.0$, 18.6, 31.8, 49.1, 52.9, 118.0, 156.3; MS (EI): $m/z = 156$, 115, 114, 99, 82, 74, 61, 59, 55, 54, 45; IR (film): 3324, 2969, 2880, 2245, 1712, 1530, 1467, 1393, 1373, 1336, 1271, 1197, 1150, 1099, 1038, 983, 953, 887, 841, 814, 781, 716, 617, 479 cm^{-1}; HRMS: $C_{11}H_{21}N_3O$: calcd 156.0899; found 156.0898.
15. All new compounds showed characteristic spectroscopic data (NMR, MS, IR) and correct HRMS or elemental analyses.