Stereoselective Complete Reduction of α-Alkyl-β-ketonitriles to *anti* γ-Amino Alcohols

Antonio De Nino,*[a] Renato Dalpozzo,[a] Giovanna Cupone,[a] Loredana Maiuolo,[a] Antonio Procopio,[a] Antonio Tagarelli,[a] and Giuseppe Bartoli[b]

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The one-pot reduction of α-alkyl-β-ketonitriles to *anti* γ-amino alcohols can be efficiently performed by borane/dimethyl sulfide complex in the presence of cerium chloride as Lewis acid. Selectivities are slightly worse than monoreduction but this drawback is overcome by much better yields.

Introduction

In the past few years we have established that the reduction of bidentate carbonyl compounds proceeds via complex chelate intermediates when BH_3 in the presence of $TiCl_4$ is used, whereas with $LiBH_4$ in the presence of $CeCl_3$, the same reaction proceeds via nonchelate intermediates whose stereochemistry can be predicted by the Felkin−Anh model.[1−6]

We have recently also accomplished the diastereoselective reduction of α-alkyl-β-ketonitriles either to *syn*- or *anti*-α-alkyl-β-hydroxynitriles by using the former or the latter methodology, respectively.[7]

The structural unit of a 1,3-amino alcohol is present with a stereodefined geometry in many compounds of biological interest.[8−12] In addition, 1,3-aminols are useful building blocks in the synthesis of many natural products.[13−16]

We envisaged that the one-pot complete reduction of readily available α-alkyl-β-ketonitriles could be an adequate approach to 1,3-aminols. Such a procedure could overcome the major drawback of the reduction of ketoamides: the uncleavable alkyl groups protecting the nitrogen atom.[6]

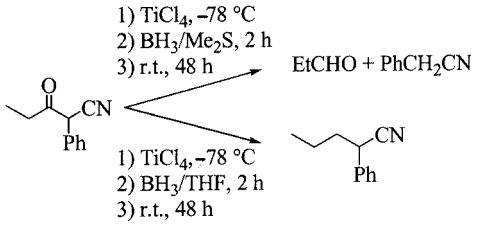
The only methods reported in the literature for the synthesis of 1,2-*syn*-3-aminols are the regio- and stereoselective ring opening of epoxyamines with alanes[17] and the acidic hydrolysis of certain 3,6-dihydro-2*H*-1,3-oxazines.[18] These procedures show good stereoselectivity, but they are rather complex as they are based on multistep reactions.

[a] Dipartimento di Chimica, Università della Calabria,
ponte Bucci cubo 15/c, 87030 Arcavacata di Rende, Italy
Fax: (internat.) +39-098/449-2055
E-mail: denino@unical.it
[b] Dipartimento di Chimica Organica 'A.Mangini', Università di Bologna,
viale Risorgimanto 4, 40136 Bologna, Italy
Fax: (internat.) +39-051/209-3654
E-mail: bartoli@ms.fci.unibo.it

1,2-*anti*-3-Aminols are often obtained by the reduction of *anti*-α-alkyl-β-hydroxynitriles, which, in turn, are generated from the aldol-type reaction of lithiated nitriles and aldehydes, whose selectivity is good only for very bulky substituents.[19] Alternatively, they are sometimes obtained from a two-step procedure which requires the concomitant microbial reduction and α-alkylation of benzoylacetone followed by LAH reduction.[20]

Results and Discussion

Borane was the reducing agent of choice for the diastereoselective reduction of α-alkyl-β-ketonitriles. The reduction of nitriles with borane and its complexes has been reported previously;[21] we rationalised the higher yields in mono-reduced products obtained with $LiBH_4$ in terms of the higher chemoselectivity of the reduction.[7] Borane complexes with amines were discarded to overcome the obvious separation difficulties with the final product also being an amine. The reaction was therefore carried out with BH_3/Me_2S or BH_3/THF complexes. Both $TiCl_4$ and $CeCl_3$ were tested as the promoting Lewis acid under chelating or nonchelating conditions, respectively. However, complete reduction under chelating conditions was unsuccessful, and only



Scheme 1

carbonyl reduction occurred at low temperature. At room temperature or higher, 3-hydroxy-2-phenylpentanonitrile, arising from the mono-reduction of 3-oxo-2-phenylpentanonitrile undergoes a retro-aldol reaction to form propionaldehyde and phenylacetonitrile using $BH_3/Me_2S/TiCl_4$ reducing systems, while $BH_3/THF/TiCl_4$ leads to an elimination/reduction pathway to 2-phenylpentanonitrile (Scheme 1). β-Hydroxynitriles are known to be sensitive to base,[19] although complete reduction to aminols has been reported in the presence of borane in THF.[22]

Complete reduction to aminols under nonchelating conditions occurred in the presence of the $BH_3/Me_2S/CeCl_3$ reducing system, with generally very high yields (Table 1). When R^1 = Et and R^2 = Ph, the low yield can be ascribed to an ineffective extraction of the product from water. Conversely, from ketoamides[6] the same reaction carried out with the BH_3/THF complex proceeded badly and elimination products were again recovered.

Table 1. Complete reduction of α-ketonitriles in the presence of $CeCl_3$ and BH_3/Me_2S

Entry	R^1	R^2	Product	Yield[a] (%)	*anti*/*syn*[b]
1	Ph	Me	2a	>99	76:24
2	Ph	Et	2b	87	75:25
3	Ph	Pr	2c	94	76:24
4	Ph	*i*Pr	2d	88	51:49
5	Me	Ph	2e	69	73:27
6	Et	Ph	2f	60	80:20
7	*i*Pr	Ph	2g	80	71:29
8	*t*Bu	Ph	2h	>99	76:24

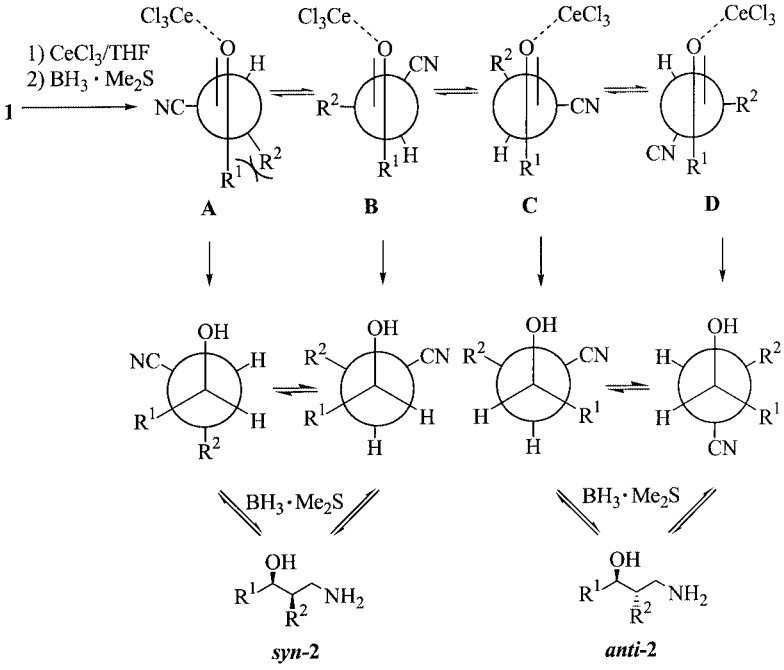
[a] Calculated after isolation by preparative TLC on the whole portion containing **2a**−**h**. [b] *syn* and *anti* refers to the racemic mixture throughout the text.

Yields are generally higher than those previously reported in the mono-reduction of the same substrates and confirm that complete reduction was then the main side reaaction.[7]

As expected, the *anti* isomer prevails over all the other reactions, according to a Felkin−Anh model of a nonchelating first-step transition state (Scheme 2). With small R^2 groups, the most electron-withdrawing cyano group assumes the orthogonal position in the Felkin−Anh model. Conformation **C** prevails over conformation **A** due to the lower steric strain, leading to *anti* selectivity. The Felkin−Anh model also accounts for the lack of selectivity for compound **1d**. In fact, on increasing the steric bulk of the R^2 group, the population of conformations **B** and **D** increases to overcome the strain caused by a complexed oxygen atom or R^1 group (see conformations **C** and **A**, Scheme 2).

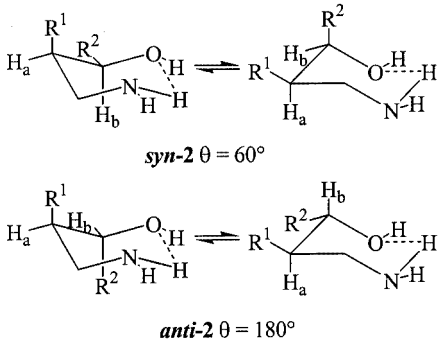
Diastereoselectivity trends in both mono and complete reductions are superimposable,[7] but *anti*/*syn* ratios are now generally lower than the corresponding ones in the synthesis of β-hydroxynitriles. This finding can be ascribed to the much higher temperature (0 °C vs. −78 °C), the longer reaction times (48−96 h vs. 2 h) and to the different reducing agent (BH_3/Me_2S vs. $LiBH_4$) necessary for the occurrence of the reaction.

Compound identification was made by comparison of the vicinal coupling constants. It is well-established that both *syn* and *anti* isomers should form as chair-shaped molecules (Scheme 3), owing to the strong intramolecular hydrogen bond between the amino and the hydroxy functions.[23] In the most stable conformation, the *anti* isomer



Scheme 2

would have H_a and H_b in a diaxial relationship, giving rise to a larger coupling constant than the *syn* isomer, which will have H_a and H_b in an axial-equatorial relationship in both conformations. On this basis, the larger coupling constant is always assigned to the *anti* isomer.[19,20,23] Therefore we assigned an *anti* relationship to the compounds showing the largest coupling constant (Table 2).



Scheme 3. A hydrogen bond should occur between the H linked to O and N without affecting the H_a/H_b relationship in both isomers

Table 2. Vicinal coupling constants for *anti* and *syn* isomers

Product	J_{anti} (Hz)	J_{syn} (Hz)
2a	7.9	3.4
2b	6.5	3.3
2c	6.2	2.8
2d	6.5	4.5
2e	6.2	5.2
2f	5.3	4.4
2g	3.0	1.3
2h	6.8	2.3

Conclusion

The preparation of *anti*-2-alkyl-1,3-aminols in a rather diastereoselective manner by reduction of α-alkyl-β-ketonitriles with the $BH_3/Me_2S/CeCl_3$ system is now available. This methodology shows many advantages with respect to known methods:[19,20]

i) The starting materials are easily available from the trivial addition of esters to nitrile enolates;

ii) The reaction conditions do not require special equipment, only an inert atmosphere;

iii) This is a one-pot reaction rather than the previous multistep synthesis.

Finally, *anti* selectivity is indeed better than in previously reported synthese with small alkyl groups,[19,20] and this reaction completes both the reduction of ketoamides (which is *syn*-selective and with uncleavable nitrogen protecting groups)[6] and the monoreduction of ketonitriles already reported by us.[7]

Experimental Section

General Remarks: ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions with a Bruker WM 300 spectrometer at 300 and at 75 MHz respectively. Chemical shifts are given in ppm from TMS, coupling constants (*J*) are given in Hertz. Mass spectra and GC were recorded with a Hewlett−Packard workstation, consisting of a HP 5890 gas chromatograph and a HP 5975 mass detector. Chemicals were purchased from Aldrich. THF was distilled twice under nitrogen over sodium wires and then over sodium/benzophenone until the blue colour persisted. α-Alkyl-β-ketonitriles (except for α-acetylphenylacetonitrile, which is commercially available) were prepared from the lithium enolate of the corresponding commercial nitrile and the appropriate commercial esters. $CeCl_3 \cdot 7H_2O$ was dried by a standard method.[24]

Reduction of α-Alkyl-β-ketonitriles with BH_3/SMe_2 in the Presence of Dry Cerium(iii) Chloride. General Procedure: A THF (10 mL) solution of α-cyanoketone (2.89 mmol) was dropped into a stirred THF (15 mL) suspension of dry $CeCl_3$ (3.47 mmol) at 0 °C under nitrogen. After 1 h BH_3/SMe_2 complex (11.56 mmol) was added dropwise. The reaction was allowed to stir for 48−96 h before quenching with H_2O/HCl (9:1). After 30 min the pH was adjusted to 11−12 with an NaOH solution, and the mixture was extracted three times with ethyl acetate. The organic layer was dried over Na_2SO_4, the solvents evaporated under reduced pressure and submitted to preparative TLC separation (eluent chloroform/methanol, 9:1). Preparative TLC allowed the separation of two portions: one containing pure *anti* isomer accounting for about 70% of the yields reported in Table 1, and the other as a mixture of *syn*/*anti* isomers accounting for the remaining 30%. The reduction of **1e** was scaled up to 10 mmol without substantial modification of yield or isomer ratio. Column separation of the isomers was much more difficult. 3-Hydroxy-2-methyl-3-phenylpropanylamine (**2a**),[22] 2-ethyl-3-hydroxy-3-phenylpropanylamine (**2b**),[20] 3-hydroxy-3-phenyl-2-propylpropanylamine (**2c**),[20] 3-hydroxy-4,4-dimethyl-2-phenylpentanylamine (**2h**),[19] showed physical data identical to the reported values. Physical data for unknown compounds are reported below (the NMR signals of *syn* isomers were assigned from the spectrum of the mixture by subtracting the signals of the pure *anti* isomer).

3-Hydroxy-2-isopropyl-3-phenylpropanylamine (2d): Oil. MS: *m*/*z* (%) = 193 (1), 176 (15), 146 (36), 133 (48), 131 (100), 120 (10), 77 (30), 55 (21), 43(7). $C_{12}H_{19}NO$ (193.3): calcd. C 74.57, H 9.91, N 7.25; found C 74.60, H 9.90, N 7.30. *anti* isomer: ^{1}H NMR: δ = 0.96 (d, *J* = 6.15 Hz, 3 H, CH_3), 0.98 (d, *J* = 6.55 Hz, 3 H, CH_3), 1.62−1.76 [m, 2 H, CH_3CHCH_3, $(CH_3)_2CHCH$], 2.66 (dd, *J* = 13.11, 9.00 Hz, 1 H, CH_2), 2.87 (dd, *J* = 13.11, 5.32 Hz, 1 H, CH_2), 3.00 (br. s, 3 H, NH_2, OH), 4.90 (d, *J* = 6.55 Hz, 1 H, C*H*-OH), 7.20−7.40 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 19.34 (CH_3), 22.30 (CH_3), 26.58 (CH_3CHCH_3), 39.82 (CH), 52.06 (CH_2-NH_2), 76.57 (*C*H-OH), 126.33, 126.72, 127.93, 143.55 (ArC) ppm. *syn* isomer: ^{1}H NMR: δ = 0.76 (d, *J* = 6.96 Hz, 3 H, CH_3), 0.86 (d, *J* = 6.96 Hz, 3 H, CH_3), 1.62−1.76 [m, 2 H, CH_3CHCH_3, $(CH_3)_2CHCH$], 3.10 (br. s, NH_2, OH), 2.86 (dd, *J* = 12.70, 8.60 Hz, 1 H, CH_2), 2.95 (dd, *J* = 12.70, 2.87 Hz, 1 H, CH_2), 4.94 (d, *J* = 4.51 Hz, 1 H, C*H*-OH), 7.20−7.40 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 18.32 (CH_3), 21.56 (CH_3), 25.79 (CH_3CHCH_3), 39.74 (CH), 51.12 (CH_2-NH_2), 76.40 (*C*H-OH), 126.29, 126.84, 128.01, 145.02 (ArC) ppm.

3-Hydroxy-2-phenylbutanylamine (2e): Oil. MS: *m*/*z* (%) = 147 (3) [$M^+ - H_2O$], 120 (5), 118 (100), 104 (21), 91 (16), 77 (9), 65 (5), 51 (3), 43 (5). $C_{10}H_{15}NO$ (165.2): calcd. C 72.69, H 9.15, N 8.48; found C 72.65, H 9.15, N 8.50. *anti* isomer: ^{1}H NMR: δ = 0.96 (d, *J* = 6.24 Hz, 3 H, CH_3), 2.54 (dt, *J* = 5.35, 9.05 Hz, 1 H, CH-Ph), 3.00−3.30 (m, 5 H, NH_2, OH, CH_2), 4.11 (dq, *J* = 6.23, 9.05 Hz, 1 H, C*H*-OH), 7.00−7.40 (m, 5 H, ArH) ppm. ^{13}C NMR: δ =

22.35 (CH_3), 46.97 (CH_2), 54.76 (CH-Ph), 73.06 (*C*H-OH), 126.60, 127.91, 128.50, 141.27 (ArC) ppm. *syn* isomer: ^{1}H NMR: δ = 1.14 (d, *J* = 6.24 Hz, 3 H, CH_3), 2.72 (dt, *J* = 7.22, 5.25 Hz, 1 H, CH-Ph), 3.00−3.30 (m, 5 H, NH_2, OH, CH_2), 4.09 (m, 1 H, C*H*-OH), 7.00−7.40 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 20.43 (CH_3), 43.56 (CH_2), 54.89 (CH-Ph), 69.96 (*C*H-OH), 126.80, 128.46, 128.97, 139.85 (ArC) ppm.

3-Hydroxy-2-phenylpentanylamine (2f): Oil. MS: *m*/*z* (%) = 161 (2) [$M^+ - H_2O$], 132 (85), 117 (100), 104 (40), 91 (25), 77 (11). $C_{11}H_{17}NO$ (179.3): calcd. C 73.70, H 9.56, N 7.81; found C 73.60, H 9.50, N 7.80. *anti* isomer: ^{1}H NMR: δ = 0.87 (t, *J* = 7.33 Hz, 3 H, CH_3), 1.10−1.30 (m, 2 H, CH_2), 2.25 (br. s, 3 H, NH_2, OH), 2.59 (dt, *J* = 5.32, 8.87 Hz, 1 H, CH-Ph), 3.14 (d, *J* = 8.87 Hz, 2 H, CH_2), 3.80−3.94 (m, 1 H, C*H*-OH), 7.10−7.50 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 17.43 (CH_3), 35.18 (CH_2), 53.87 (CH_2), 60.33 (CH-Ph), 84.93 (*C*H-OH), 134.08, 135.44, 136.25, 149.60 (ArC) ppm. *syn* isomer: ^{1}H NMR: δ = 0.94 (t, *J* = 7.32 Hz, 3 H, CH_3), 1.32−1.47 (m, 2 H, CH_2), 2.70−2.80 (m, 4 H, NH_2, OH, CH-Ph), 3.08 (d, *J* = 4.30 Hz, 2 H, CH_2), 3.80−3.90 (m, 1 H, C*H*-OH), 7.10−7.50 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 16.88 (CH_3), 35.80 (CH_2), 52.44 (CH_2), 60.44 (CH-Ph), 81.89 (*C*H-OH), 135.44, 136.00, 136.32, 141.00 (ArC) ppm.

3-Hydroxy-4-methyl-2-phenylpentanylamine (2g): Oil. MS: *m*/*z* (%) = 175 (1) [$M^+ - H_2O$], 162 (2), 146 (70), 131 (100), 104 (20), 91 (18). $C_{12}H_{19}NO$ (193.3): calcd. C 74.57, H 9.91, N 7.25; found C 74.60, H 9.95, N 7.25. *anti* isomer: ^{1}H NMR: δ = 0.77 (d, *J* = 6.78 Hz, 3 H, CH_3), 0.85 (d, *J* = 6.96 Hz, 3 H, CH_3), 1.20−1.40 (m, 1 H, $CHMe_2$), 1.92 (br. s, 3 H, NH_2, OH), 2.90−3.13 (m, 3 H, CH_2CHPh), 3.48 (dd, *J* = 3.03, 9.81 Hz, 1 H, C*H*-OH), 7.10−7.30 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 14.26 (CH_3), 30.16 (CH_3), 39.74 (CH), 45.48 (CH_2), 50.21 (CH-Ph), 79.36 (*C*H-OH), 126.10, 127.92, 128.54, 139.61 (ArC) ppm. *syn* isomer: ^{1}H NMR: δ = 0.79 (d, *J* = 6.53 Hz, 3 H, CH_3), 0.95 (d, *J* = 6.61 Hz, 3 H, CH_3), 1.20−1.40 (m, 1 H, $CHMe_2$), 1.92 (br. s, 3 H, NH_2, OH), 2.90−3.13 (m, 3 H, CH_2CHPh), 3.84 (dd, *J* = 1.29, 9.82 Hz, 1 H, C*H*-OH), 7.10−7.30 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 17.95 (CH_3), 31.10 (CH_3), 43.01 (CH), 47.18 (CH_2), 50.36 (CH-Ph), 80.64 (*C*H-OH), 126.54, 128.37, 129.48, 141.40 (ArC) ppm.

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