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HIGHLY DIASTEREOSELECTIVE ADDITION OF CYANIDE TO β-HYDROXYKETONES

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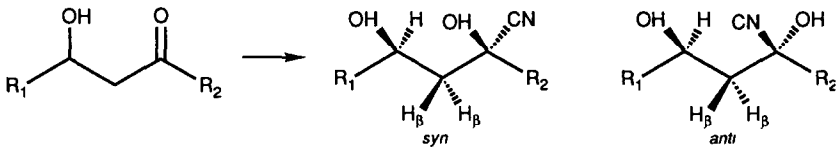
Abstract: The addition of cyanide with KCN/ZnI_2/TMSCN to β-hydroxyketones (R_1-CHOH-CO-R_2, R_1 = *i*-Pr, R_2 = Me, Et, *i*-Bu, *i*-Pr, *t*-Bu, R_1= Et, R_2 = *t*-Bu and R_1 = Bn, Ph, R_2 = *i*-Bu) produced *syn* β-hydroxycyanohydrins in 95% d.e.

The stereoselective production of 1,3-diols is of increasing importance in natural product synthesis.[1] While the reduction of β-hydroxyketones has been recently described to proceed with high diastereomeric excess (d.e.),[2] the only example found in the literature concerning addition of CN^- to these compounds yielded a extremely low d.e. (4%).[3] In contrast, we hereby report (Table 1) that high d.e.'s and good chemical yields were obtained in the addition of cyanide to β-hydroxyketones when the reaction was carried out with KCN/ZnI_2/TMSCN.[4]

Table 1. *- Results of cyanide addition (KCN/ZnI_2/TMSCN) to β-hydroxyketones.*



Entry	R_1	R_2	d e (%)	δ_{CHOH} major/minor[a] (ppm) ^{13}C	^1H
1	*i*-Pr	Me	>95	75.8/72.6	4.10/3.75
2	"	Et	>95	76.0/73.0	4.00/3.80
3	"	*i*-Bu	90	75.6/73.3	4.10/3.80
4	"	*i*-Pr	>95	75.9/73.1	4.20/3.80
5	"	*t*-Bu	>95	75.6/	4.10/3.80
6	Et	*t*-Bu	95	72.4/70.5	4.12/3.85
7	Bn	*i*-Bu	>95	71.7/69.6	4.50/4.25
8	Ph	"	>95	73.8/70.9	5.38/5.10

[a] See text

The % d.e. has been determined in the crude reaction mixture, prior to any purification, by integration of the methine proton at *ca.* 3.8 - 5.4 ppm (Table 1). The absence of the minor isomer was confirmed by comparison with control spectra from the same reaction performed without solvent in the presence of 18-crown-6,[3] instead of ZnI_2, which gave variable d.e.'s in the range of 20-90% and therefore allowed us to isolate both isomers by flash chromatography .

The homogeneous ^{13}C- and ^{1}H-nmr data of CHOH group collected in Table 1 ($\delta_{major} > \delta_{minor}$) suggests that the predominant isomer bears the same configuration in all the cases. We have asigned the *syn* and *anti* configurations to the major and minor isomers, respectively, from 2D-nmr COLOC experiments[5] (200 MHz) tuned for antiperiplanar $^{3}J_{CH}$ (8 Hz), observing the correlation of CN carbon with the β-protons.[6] Considering that the reaction is kinetically controlled,[7] the predominant production of the *syn* isomer may be easily justified in terms of the greater stability of the chair like transition state (ET1 in Figure 1) leading to this isomer.[8]

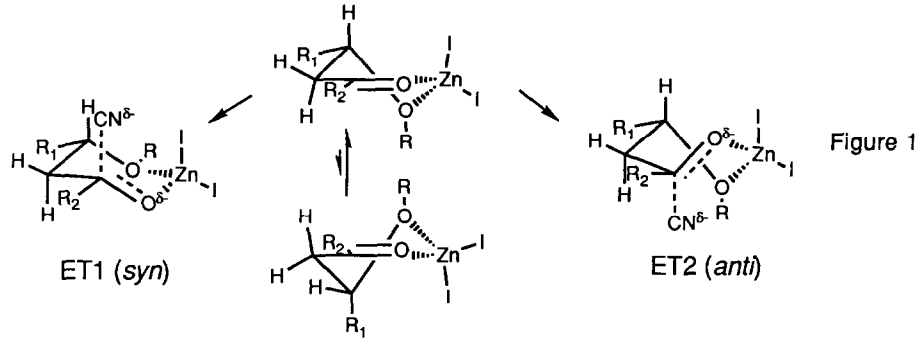


Figure 1

Further research concerning production of the *anti* isomer in high d.e. and the transformation of the CN group of the resulting β-hydroxycyanohydrins is under way.

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References and Notes

1. See for example Omura, S.; Tanaka, H. "Macrolide Antibiotics: Chemistry, Biology and Practice", Omura, S. Ed. Academic Press, p. 351-404 (1984).

2. Evans, D.A.; Hoveyda, A.H. *J. Org. Chem.* **1990**, *55*, 5190 and references cited therein.

3. Rychnovsky, S.D.; Zeller, S.; Skalitzky, D.J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550; the addition was performed with TMSCN/CN^-/18-crown-6 but no experimental details were given.

4. To 5 mmol of β-hydroxyketone in 10 ml of CH_2Cl_2, 0.33 g (5 mmol) of KCN and 1.59 g (5 mmol) of ZnI_2 were added and the mixture was stirred (20 min.) under Ar at room temperature. A solution of 1.24 g (12.5 mmol) of TMSCN in 10 ml of CH_2Cl_2 was injected at 0°C and the mixture stirred overnight at 0°C. The reaction was quenched with 1.5 ml of conc. HCl and diluted with 50 ml of water. The organic layer, together with 2x25 ml CH_2Cl_2 extracts of the aqueous phase, was dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by flash chromatography (ethyl acetate/hexane 5:1). Average yield 75%.

5. Kessler, H.; Griesinger, C.; Zarbock, J.; Loosli, H.R. *J. Magn Reson.* **1984**, *57*, 331.

6. If the most stable conformers of isomers *syn* and *anti* are those depicted in Table 1 (MMP2 calculations supported this assumption), CN is always *anti* and *gauche* ($^{3}J_{CH}$ *ca.* 8 and 2 Hz, respectively) to the β-protons. On the other hand, the Hβ *anti* to CN is also *anti* to CHOH in the *syn* isomer but *gauche* in the *anti* isomer. In the COLOC experiment we observed that CN of major isomer of entries 3 and 5 (Table 1) correlated only with the β-proton bearing a $^{3}J_{HH}$ of *ca.* 10 Hz with the methine CHOH proton (*i e.* C/Hβ and Hβ/CHOH are antiperiplanar as in *syn* isomer) whereas, in the minor isomer of entries 3 and 7 (Table 1), the CN did so with the β-proton coupled to the CHOH proton with $^{3}J_{HH}$ of *ca.* 3 Hz (i.e. C/Hβ are also *anti* but Hβ/CHOH are *gauche* as in *anti* isomer). Unfortunately, this analysis could not be performed in the other cases due to the very small chemical shift difference (<15 Hz) observed between geminal β-protons.

7. Evans, D.A.; Carrol, G.L.; Truesdale, L.K. *J. Org. Chem.* **1974**, *39*, 914.

8. In contrast, the corresponding intermolecular hydride addition, which also gives the *syn* isomer as the major component (Narasaka *et al Tetrahedron* **1984**, *40*, 2233), has been explained by the higher hindrance exerted by the pseudoaxial α-proton to carbonyl, in the H^- approach to the lower C=O face. Our MMP2 calculations, following a method similar to that described elsewhere (Wuts *et. al. J. Org. Chem.* **1984**, *49*, 4573), predicted that the upper face is in turn sterically more hindered to CN access and thus, it did not support the latter explanation.

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