Optically Active (*S*)-Ketone- and (*R*)-Aldehyde-cyanohydrins *via* an (*R*)-Oxynitrilase-catalysed Transcyanation. Chemoenzymatic Syntheses of 2-Cyanotetrahydrofuran and 2-Cyanotetrahydropyran

Emma Menéndez, Rosario Brieva, Francisca Rebolledo and Vicente Gotor*

Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, 33071 Oviedo, Spain

(*R*)-Oxynitrilase catalyses the enantioselective decyanation of racemic ketone cyanohydrins and the enantioselective addition of HCN to ω-bromoaldehydes in one step.

Optically active cyanohydrins are valuable starting materials for the synthesis of a great variety of interesting compounds such as α-hydroxy acids, α-hydroxy aldehydes, β-amino alcohols and α-amino acids. One of the most used methods for the synthesis of enantiopure cyanohydrins is the oxynitrilase-catalysed enantioselective addition of hydrogen cyanide to aldehydes or ketones.[1] (*R*)-Oxynitrilase from almonds has been used to catalyse this reaction with aromatic and aliphatic aldehydes,[2] and also with aliphatic ketones,[3] giving the corresponding (*R*)-cyanohydrins. Some procedures have been developed in order to avoid the competing non-enzymatic reaction and obtain cyanohydrins with high enantiomeric excesses; for example, the use of water non-miscible organic solvents,[2] or the use of acetone cyanohydrin as cyanide source to keep a low concentration of HCN in the reaction.[4]

In addition, two (*S*)-oxynitrilases from *Sorghum bicolor* and from the leaves of *Hevea brasiliensis* have proved to catalyse the formation of (*S*)-cyanohydrins from aromatic[5] and aliphatic[6] aldehydes, respectively. However, the enantioselective synthesis of (*S*)-ketone cyanohydrins has not yet been achieved using this methodology.

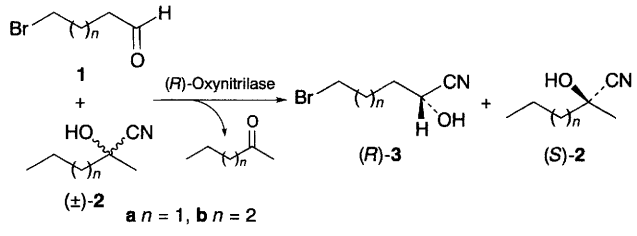
Since (*R*)-oxynitrilase catalyses either the HCN elimination from acetone cyanohydrin[4] and the enantioselective HCN addition to some aliphatic ketones,[3] it is expected that (*R*)-oxynitrilase preferably catalyses the HCN elimination from the (*R*)-enantiomer of a racemic ketone cyanohydrin, making possible the isolation of the unreacted (*S*)-ketone cyanohydrin. This idea, and the importance of optically pure ω-bromocyanohydrins as starting materials for some heterocycles, prompted us to investigate the enzymatic transcyanation reaction between ω-bromoaldehydes **1** and racemic ketone cyanohydrins **2**.

The reactions are carried out in diisopropyl ether using a crude extract of almond containing (*R*)-oxynitrilase as the catalyst.[4b] Two different molar ratios aldehyde : ketone cyanohydrin, 1 : 1.5 and 1 : 2, are used in order to optimise the reaction conditions for the two processes (Scheme 1). The results are collected in Table 1. All reactions are allowed to proceed until compounds **1** are completely transformed into the corresponding ω-bromocyanohydrin **3**.

The results obtained clearly indicate that (*R*)-oxynitrilase is an efficient catalyst for the HCN addition to ω-bromoaldehydes, ω-bromocyanohydrins being obtained with high enantiomeric excesses. As a general rule, the enzyme shows comparable enantioselectivity with both aldehydes independently of the ketone cyanohydrin used as cyanide donor.†

However, the results obtained in the resolution of compounds **2** indicate an appreciable influence of the aldehyde in the enantioselectivities of the decyanation processes, particularly the excellent optical purities obtained for **2b** in the reactions with **1b** (entries 7 and 8). In absence of the aldehyde, the (*R*)-oxynitrilase-catalysed decyanation of (±)-**2b** is very slow and, for a conversion of 55% (attainable after ten days), the remaining cyanohydrin is racemic, probably due to the reversibility of the process. Therefore, it is clear that the presence of the aldehyde as cyanide receptor is crucial to avoid the reversible decyanation of the ketone cyanohydrins **2** and, consequently, to achieve their resolution with good enantioselectivities.‡

Finally, the optically active ω-bromocyanohydrins **3** obtained are easily transformed into the corresponding (*R*)-2-cyanotetrahydrofuran **4a** and (*R*)-2-cyanotetrahydropyran **4b**§ by a simple cyclization with silver perchlorate (Scheme 2), in which no racemization is observed.¶ These functionalized tetrahydrofurans and tetrahydropyrans are important since they are common structural components of interesting compounds such as terpenoids, pheromones, antibiotics, *C*-glycosides and other biologically active natural products.[9]

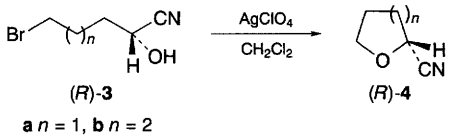


Scheme 1

Table 1 Enzymatic transcyanation of ω-bromoaldehydes **1** and racemic ketone cyanohydrins **2**[a]

				(*R*)-**3**			(*S*)-**2**		
Entry	**1**	**2**	Ratio **1**:**2**		Yield (%)[b]	E.e. (%)[d]		Yield (%)[b,c]	E.e. (%)[d]
1	**1a**	**2a**	1:1.5	**3a**	81	92	**2a**	78	51
2	**1a**	**2a**	1:2	**3a**	82	88	**2a**	76	66
3	**1a**	**2b**	1:1.5	**3a**	79	75	**2b**	84	70
4	**1a**	**2b**	1:2	**3a**	83	83	**2b**	81	89
5	**1b**	**2a**	1:1.5	**3b**	73	90	**2a**	71	80
6	**1b**	**2a**	1:2	**3b**	70	89	**2a**	75	55
7	**1b**	**2b**	1:1.5	**3b**	81	91	**2b**	75	>95
8	**1b**	**2b**	1:2	**3b**	78	87	**2b**	77	>95

[a] Reaction conditions: see ref. 4*b*. Reaction time for **1a** is 12 h and for **1b** is 24 h. [b] Calculated from the recovered product after purification by column chromatography. Eluent: hexane–dichloromethane–ethyl acetate 5.5 : 2.5 : 1. [c] Yields for compounds **2** are calculated taking into account that 100% of conversion of **1** into **3** is achieved in all the reactions. [d] Determined by derivatization with Mosher's acid chloride followed by ^{19}F NMR (188 MHz) analysis and comparison with the diastereomeric esters prepared from their racemic counterparts. For **2a** $[\alpha]_D^{22}$ −1.1 (*c* 1.05, $CHCl_3$), 80% e.e.; for **2b** $[\alpha]_D^{22}$ −3.8 (*c* 0.93, $CHCl_3$), >95% e.e.; for **3a** $[\alpha]_D^{22}$ +16.1 (*c* 1.0, $CHCl_3$), 92% e.e.; for **3b** $[\alpha]_D^{22}$ +10.7 (*c* 1.0, $CHCl_3$), 91% e.e.



(*R*)-**3** (*R*)-**4**

a $n = 1$, **b** $n = 2$

Scheme 2

We are grateful to the Dirección General de Investigación Científica y Técnica (Project BIO 92-0751) for financial support.

Received, 23rd January 1995; Com. 5/00393H

Footnotes

† Similar results are also obtained with acetone cyanohydrin.

‡ (*S*)-Configurations of compounds **2** are assigned as follows: conventional acetylation of (−)-**2a** (Table 1, entry 6) yields 1-cyano-1-methylbutyl acetate, $[\alpha]_D^{22}$ −8.1 (*c* 0.92, C_6H_6), 55% e.e. By comparison with published data[7] for (*S*)-1-cyano-1-methylbutyl acetate, $[\alpha]_D^{26}$ −15.0, (*c* 1.32, C_6H_6), >95% e.e., we established the (*S*)-configuration for (−)-**2a**. Compound (−)-**2b** is assumed to have the (*S*)-configuration by comparison of the ^{19}F NMR signals of the Mosher's esters derivatives of (−)-**2a** and (−)-**2b** with those of (±)-**2a** and (±)-**2b**; in both cases the lower field signal disappears in the spectra of the optically active cyanohydrins.

§ (*R*)-Configuration for **4a** and **4b** is assigned as follows: sulfuric acid-mediated hydrolyses of (−)-**4a** and (−)-**4b** lead to (+)-tetrahydrofuran-2-carboxylic acid and (+)-tetrahydropyran-2-carboxylic acid, respectively, which have been reported to have (*R*)-configuration.[8] In this way, we have also assumed the (*R*)-configuration for the starting ω-bromocyanohydrins **3**.

¶ The enantiomeric excess for compound **4a** (92%, $[\alpha]_D^{22}$ −26.1, *c* 0.85, $CHCl_3$) is determined by ^1H NMR (200 MHz) using as chiral shift reagent $Eu(tfc)_3$, this is the same value as for its precursor **3a**. The e.e. for compound **4b** ($[\alpha]_D^{22}$ −32.9, *c* 0.77, $CHCl_3$) is assumed to be the same as the starting bromocyanohydrin **3b**, *i.e.* 91%.

References

1 F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1555; M. North, *Synlett*, 1993, 807.
2 F. Effenberger, T. Ziegler and S. Förster, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 458; T. Ziegler, B. Hörsch and F. Effenberger, *Synthesis*, 1990, 575.
3 F. Effenberger, B. Hörsch, F. Weingart, T. Ziegler and S. Kühner, *Tetrahedron Lett.*, 1991, **32**, 2605.
4 (*a*) V. I. Ognyanov, V. K. Datcheva and K. S. Kyler, *J. Am. Chem. Soc.*, 1991, **113**, 6992; (*b*) T. T. Huuhtanen and L. T. Kanerva, *Tetrahedron Asymmetry*, 1992, **3**, 1223.
5 F. Effenberger, B. Hörsch, S. Förster and T. Ziegler, *Tetrahedron Lett.*, 1990, **31**, 1249; U. Niedermeyer and M.-R. Kula, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 386.
6 N. Klempier, H. Griengl and M. Hayn, *Tetrahedron Lett.*, 1993, **34**, 4769.
7 H. Ohta, Y. Kimura, Y. Sugano and T. Sugai, *Tetrahedron*, 1989, **45**, 5469.
8 E. Fritz-Langhals, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 753; O. Cervinka, O. Bajanzulyn, A. Fábryová and A. Sackus, *Collect. Czech. Chem. Commun.*, 1986, **51**, 404.
9 C. Mukai, Y. Sugimoto, Y. Ikeda and M. Hanaoka, *J. Chem. Soc., Chem. Commun.*, 1994, 1161; M. H. D. Postem, *Tetrahedron*, 1992, **48**, 8545.