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A Novel Highly Diastereoselective Synthesis of Cyano Ethers by Regioselective Ring opening of Chiral Oxazolidinium Methiodides with Sodium Cyanide.

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Key words: Chiral Oxazolidinium Iodides, alpha-Cyano Ethers, Diastereoselective Ring Opening, alpha-Hydroxy Acids, Asymmetric Synthesis.

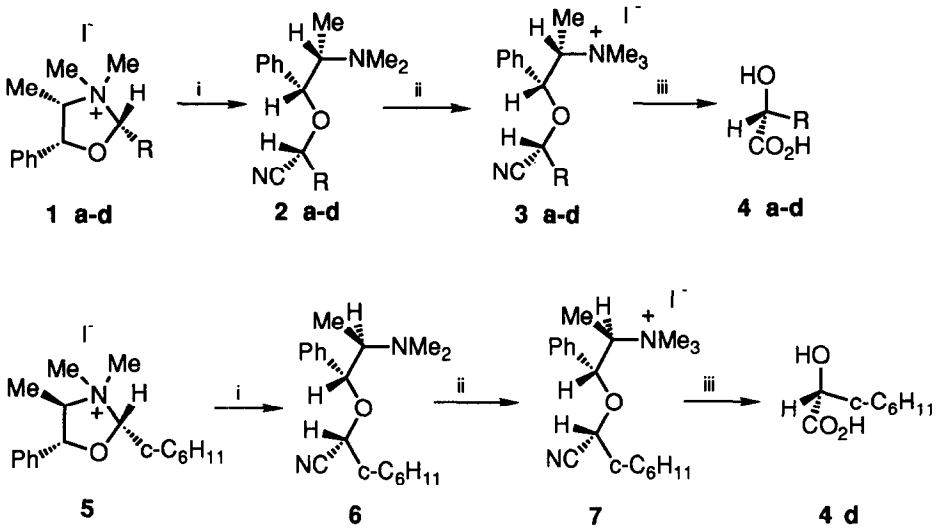
Abstract. Sodium cyanide reacts with chiral Oxazolidinium methiodides, prepared by quaternization of oxazolidines with methyl iodide, leading regio- and stereoselectively (d.e. 82-94%) to cyano ethers in moderate to good chemical yields (51-95%). The open compounds are isolated as a pure diastereomer by a single recrystallization of their ammonium methiodides, and converted into enantiomerically pure α-hydroxy acids by heting with a concentrated solution of hydrochloric acid.

Chiral cyclic N,O-acetals derived from 1,2-[1] and 1,3-aminoalcohols[2] have been widely used as adjuvants in diastereoselective transformations at C-2 side chain by electrophilic,[1] nucleophilic,[1,3] and radical-mediated reactions,[4] whereas nucleophilic ring opening of chiral oxazolidines by organometallics has been explored in the enantioselective synthesis of amines,[5,6] and α- or β-amino acid derivatives.[7,8]

Recently we have observed[9] that the regioselectivity in the ring opening of N,O-cyclic acetals changes when the nitrogen is converted into a better leaving group by transformation into their ammonium salts, and now we report on the first regio- and stereocontrolled C-N fragmentation of chiral oxazolidinium methiodides **1 a-d**[10] leading to cyanohydrine derivatives with excellent diastereoselectivity.

Control experiments revealed that oxazolidinium iodide **1a** was recovered unchanged after treatment with sodium cyanide in methanol or methanol-water (1:1, v:v) for 24 hours at reflux, but it was completly transformed into the cyanohydrine **2** after heating for 3 hours at 130°C with sodium cyanide in DMF or DMSO.

In these conditions compounds **1a-d** were converted into **2a-d** in 51-95 % yield with very high diastereoselectivity (Table 1). Because the impossibility of isolation of the major diastereomers by TLC or column chromatography, the mixture was transformed into the ammonium iodides **3** by reaction with a two fold excess of methyl iodide; a single recrystallization of the solids gave almost diastereomerically pure compounds **3a-d**,[11] as shown by ^{1}H-NMR.



Scheme 1. *Reagents and conditions*: i; NaCN, DMSO, 130°C. ii; CH_3I excess, R.T. iii; conc. HCl, reflux

Table 1. Stereoselective ring opening of **1a-d**, *ent* **1a-d**, **5** and *ent* **5** and transformation into α-hydoxy acids **4a-d** and *ent* **4a-d**

Entry	Compound (R)	2		3				4		
		Yield[a]	d.e.[b]	Yield[c]	d.e.[d]	$[\alpha]^{20}_D$	M.p.	Yield[a]	e.e.[e]	Conf.[f]
1	**1a** $CH(CH_3)_2$	55	90	86	>98	-30.9	217-218	61	>98	R
2	*ent*-**1a**	51	93	90	>98	+30.8	217-219	63	>98	S
3	**1b** $CH_2CH(CH_3)_2$	62	94	90	>98	-37.8	198-199	70	>98	R
4	*ent*-**1b**	60	93	90	>98	+38.2	197-198	72	>98	S
5	**1c** $CH_2CH_2C_6H_5$	57	94	90	>98	-35.1	175-177	64	>98	R
6	*ent*-**1c**	54	93	91	>98	+34.8	176-177	64	>98	S
7	**1d** $cycloC_6H_{11}$	92	92	90	>98	-30.8	190-191	60	>98	R
8	*ent*-**1d**	95	92	90	>98	+31.0	190-191	63	>98	S
9	**5** $cycloC_6H_{11}$	65	82	86	82	-43.8	oil	62	82	R
10	*ent*-**5**	63	84	86	84	+44.9	oil	62	84	S

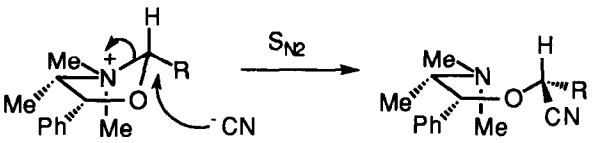
[a]The given yields are referred to pure and isolated compounds. [b]Determined by ^{13}C-NMR. [c]Referred to pure compounds after recristallyzation from EtOH. [d]Determined by ^{1}H-NMR. [e]Determined by ^{19}F-NMR in the Mosher derivatives. [f]Determined by the sign of the optical rotation previously described.

At this stage, the attempts to transform compounds **2a-d** or the salts **3a-d** into cyanohydrines by elimination of the benzyl moiety by hydrogenolysis in the presence of Pd on carbon, or by heating with ammonium formate, gave a very complex mixture of products.

Then we turned our attention to the transformation of compounds **3a-d** into α-hydroxy acids by hydrolysis of the cyano to the carboxylic group with 6N HCl in ether at 0°C[12] and subsequent hydrogenolysis, but a little racemization (3-5%) was observed during debenzylation.

In contrast, **3a-d** was hydrolyzed and debenzylated to the enantiomerically pure **4a-d** in one step by refluxing for 5-6 h with an aqueous concentrated HCl solution without any apparent racemization.[13,14] The absolute configuration of the (R)-α-hydroxy acids **4a-d** was assigned by comparison of the sign of the optical rotation with that of the known compounds,[14-17] whereas the enantiomeric excesses were determined by integration of the signals in the ^{19}F-NMR spectra for the (R)-(-)-MTPA derivatives[18] of the corresponding methyl esters.

Both the stereochemistry of the major isomers obtained and the high degree of stereoselectivity in the ring opening are explained as a consequence of a bimolecular nucleophilic displacement of the C-N bond by the cyanide ion acting from the "*oxygen face*" in the oxazolidinium salts,[19] and leading to the (R) configuration in the new stereocenter.



On the other hand, the configuration of the chiral center in the open products only depends on the stereochemistry at C-2 in the heterocycle. To prove this fact we have prepared the oxazolidinium salt (2S,4R,5R)-**5** by condensation of (1R,2R)-(-)- pseudoephedrine with cyclohexane carboxaldehyde and quaternization. Treatment of **5** with sodium cyanide gave **6** in 82% d.e., that was transformed into the oily unrecrystallizable **7** by reaction with methyl iodide; subsequent hydrolysis in the described conditions yielded (R)-α-hydroxy cyclohexylacetic acid **4d** in 82% e.e..

The (S)-α-hydroxy acids *ent*-**4a-d** are accesible in the same way using as chiral auxiliaries the (+) enantiomers of ephedrine and pseudoephedrine (Table 1).

In summary, the proposed protocol[20] constitutes a highly efficient regio- and stereoselective alternative to the usual cleavage of the the C-O bond in the neutral 1,3-oxazolidines leading to amino derivatives; in the present case, the nucleophilic displacement of the C-N bond in the oxazolidinium methiodides yields the versatile cyanohydrine derivatives with excellent d.e.

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(20) *The general experimental procedure is as follows*: A solution of oxazolidinium methiodide **1** (15 mmol) and sodium cyanide (30 mmol) in 100 ml of DMSO, under nitrogen, was heated at 130°C for 2-4 h. When the reaction was finished (TLC) the mixture was cooled, poured into 25 ml of 1N solution of NaOH and extracted with ether (3x 100 ml). The organic layer was dried over anhydrous $MgSO_4$, the solvents were removed, and the products **2** were isolated by distillation under reduced pressure or by column chromatography (silica gel, hexane/ethyl acetate = 20/1).
Formation of the ammonium salts **3**. To a stirred solution of the mixture of diastereomers **2** (10 mmol) in 25 ml of toluene at 0°C, under nitrogen, was added methyl iodide (20 mmol) and the reaction was allowed to rise to room temperature until a precipitate appeared. The solvent was eliminated by filtration, and the compounds **3** were purified by recrystallization from ethanol.
Hydrolysis to α-hydroxy acids. A solution of **3** (5 mmol) in 25 ml of concentrated HCl was heated at 60°C for 5-6 h until the reaction was finished (TLC). The mixture was extracted with ether (3x 50 ml), the organic layer was washed with $NaHCO_3$ and water, dried over anhydrous $MgSO_4$ and the solvent evaporated. The α-hydroxy acids **4** were purified by recrystallization.

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