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Easy Direct Stereo- and Regioselective Formation of β-Hydroxy Nitriles by Reaction of 1,2-Epoxides with Potassium Cyanide in the Presence of Metal Salts

Marco Chini, Paolo Crotti,* Lucilla Favero and Franco Macchia
Dipartimento di Chimica Bioorganica, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy

Key Words: β-hydroxy nitriles; epoxides opening reactions; regioselectivity; catalysts.

Abstract: *A simple efficient, anti stereoselective, and highly regioselective method for the synthesis of β-hydroxy nitriles by the direct opening of 1,2-epoxides with KCN in acetonitrile, in the presence of metal salts, is described. This new method appears to be competitive with the other methods previously reported.*

β-Hydroxy nitriles are useful intermediates in organic synthesis,[1] mainly as synthons for 1,3-amino alcohols.[2] The most direct method for obtaining these compounds is the reaction of 1,2-epoxides with hydrogen cyanide or with cyanides.[1,3] However, these methodologies appear to be applied in a satisfactory way only when simple aliphatic epoxides such as ethylene oxide are utilized.[1] When more complex epoxides are concerned, low yields of β-hydroxy nitriles are obtained even when the reaction conditions are forced.[4] Cyclohexene oxide reacts with aqueous hydrogen cyanide generated *in situ* yielding only 60% hydroxy nitrile after seven days at room temperature; furthermore, the reaction is not completely *anti*-stereoselective and certain amounts of the *cis* derivative are formed.[4c] Better results are obtained by making use of either hydrogen cyanide-triethylaluminum or diethylaluminum cyanide as hydrocyanating agents[5] or by the reaction of aqueous sodium cyanide in the presence of a catalytic amount of 12-crown-4.[6] Cyanotrimethylsilane (Me_3SiCN) has been successfully utilized for the introduction of the cyano functionality by its addition to 1,2-epoxides.[3,7-15] Due to the ambident character of Me_3SiCN, its addition to epoxides can lead either to β-hydroxy nitriles or isonitriles, depending on the type of catalyst and on the reaction conditions used. However, the judicious choice of an appropriate catalyst [3] [e.g. "hard" Lewis acid catalysts such as aluminum-containing ones,[7-9] $LnCl_3$,[10] $Ti(O\text{-}i\text{s}Pr)_4$[11,12] and $Yb(CN)_3$,[13] as CaO[14] and under potassium cyanide/18-crown-6[15] complex catalysis] selectively leads only to the nitriles. Furthermore, in the addition reaction of Me_3SiCN to epoxides, the primary reaction products are the trimethylsilyl O-protected β-hydroxy nitriles; in order to get free compounds, it is necessary to achieve deprotection. It, therefore, appears that a simple *anti*-stereoselective procedure for a direct and easy formation of β-hydroxy nitriles from epoxides is still lacking. Our discovery of a new, very efficient common metal salt-catalyzed direct aminolysis[16] and azidolysis[17] of epoxides in non-protic solvents prompted us to verify the possibility of effecting the direct addition of cyanide to epoxides under the same type of catalysis. On this basis, we have discovered a new convenient methodology for the addition of potassium cyanide to 1,2-epoxides through the catalysis of readily available metal salts, affording β-hydroxy nitriles.

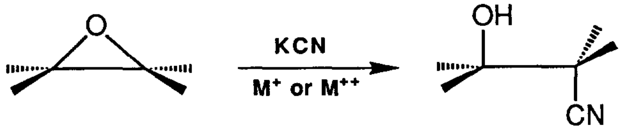
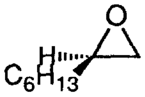
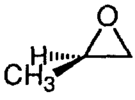
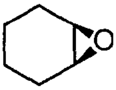
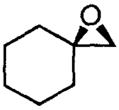
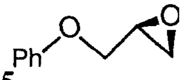
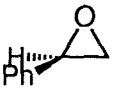
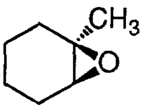
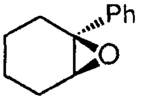


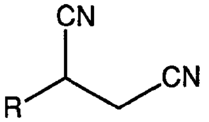
Table . Reaction of epoxides 1-8 with KCN in acetonitrile in the presence of metal salts, and under a representative acidic (NH_4Cl) condition.

entry	epoxide[a]	reagents and reaction conditions[b]		reaction time (h)	α attack[c]	β attack[d]	yield %[e]
1	 **1**	$LiClO_4$/KCN	A	8	1.8[f]	97.0[g]	95[h]
2		$Mg(ClO_4)_2$/KCN	B	8	1.8[f]	98.2[g]	95
3		NH_4Cl/KCN	C	24	2.2[f]	96.5[g]	93[h]
4	 **2**	$LiClO_4$/KCN	A	8	3.5[f]	95[i]	90[j]
5		$Mg(ClO_4)_2$/KCN	B	8	4.0[f]	93[i]	90[k]
6		NH_4Cl/KCN	C	24	3.0[f]	92[i]	94[l]
7	 **3**	$LiClO_4$/KCN	D	24	*m*		96
8		$Mg(ClO_4)_2$/KCN	B	24	*m*		48
9		NH_4Cl/KCN	C	24	*m*		91
10	 **4**	$LiClO_4$/KCN	D	8	<1	>99[n]	95
11		NH_4Cl/KCN	C	24	<1	>99[n]	94
12	 **5**	$LiClO_4$/KCN	D	4	<1	>99[o]	98
13		$Mg(ClO_4)_2$/KCN	B	24	<1	>99[o]	96
14		NH_4Cl/KCN	C	24	<1	>99[o]	96
15	 **6**	$LiClO_4$/KCN	D	24	23[p]	77[q]	95
16		$Mg(ClO_4)_2$/KCN	B	24	16[p]	84[q]	75
17		$NaClO_4$/KCN	D	48	no reaction		
18		$KClO_4$/KCN	D	48	no reaction		
19		KCN	E	72	no reaction		
20		NH_4Cl/KCN	C	24	8[p]	92[q]	95
21	 **7**	$LiClO_4$/KCN	D	48	1[f]	99[r]	95
22		$Mg(ClO_4)_2$/KCN	D	48	3[f]	97[r]	40
23		NH_4Cl/KCN	C	24	2[f]	98[r]	94
24	 **8**	$LiClO_4$/KCN	D	48	<1	>99[s]	80
25		NH_4Cl/KCN	C	48	2[f]	98[s]	90

[a] All the reactions were carried out on racemic material. [b] A, as in D with an epoxide/KCN ratio=1:1.1; B, as in D with an epoxide/metal salt ratio = 1:0.7; C, KCN (5 equiv), NH_4Cl (2.2 equiv), $MeOH/H_2O$ 8:1 (10 ml), refluxing temperature, ref. 11; D, see General Procedure; E, KCN (2 equiv), in CH_3CN (5 ml), refluxing temperature. [c] Attack of the nucleophile on the more substituted oxirane carbon.[d] Attack of the nucleophile on the less substituted oxirane carbon. [e] Yields based on weight, GLC analysis and ^1H NMR examination of the isolated crude reaction product.[f] Determined by ^1H NMR and GLC. [g] Liquid (ref.13, as TMS derivative). [h] Compound **9** present (1.2%). [i] Liquid (ref.9, as TMS derivative). [j] Compound **10** present (1.5%). [k] Compound **10** present (3.0%). [l] Compound **10** present (5.0%). [m] Solid,mp 49-50°C (ref.4c, mp 49-51°C).[n] Liquid (ref.13, as TMS derivative). [o] Solid, mp 50-51°C (ref. 15, as TMS derivative). [p] Solid, mp 63-65°C (ref.19, liquid): ^1H NMR δ 7.50-7.39 (m,5H,aromatic protons), 4.17 (unresolved triplet,1H,PhC*H*CN), 2.99 (d,1H,J=1.63 Hz,CH_AH_BOH), 2.95 (d,1H,J=2.13 Hz,CH_AH_BOH). [q] Liquid (ref.15,as TMS derivative). [r] Liquid (ref.9 as TMS derivative). [s] Solid, mp 101-102.5 °C; ^1H NMR δ 7.56-7.24 (m,5H,aromatic protons),2.96 (m,1H,CHCN), 2.48-2.33 (m,1H),2.25-2.08 (m,1H).

The reaction of 1,2-epoxides with a suspension of potassium cyanide in acetonitrile in the presence of a small molar excess of lithium perchlorate at 70°C yields in quite fair yield (≥ 90%) , in times ranging from 4 to 48 h, the corresponding β-hydroxy nitriles. The results obtained in the reaction of some representative epoxides (**1-8**) with potassium cyanide in the presence of some metal salts are shown in the Table together with the results obtained with the same epoxides under classic aqueous acidic conditions.[11] $LiClO_4$ turns out to be the most effective catalyst in this reaction, leading to higher yields than $Mg(ClO_4)_2$, while $NaClO_4$ and $KClO_4$ are not effective at all and $Zn(CF_3SO_3)_2$ (not shown in the Table) leads to complex reaction mixtures not containing the addition products.

The addition of cyanide ion to the epoxides is completely selective with the exclusive formation of nitriles, no trace of the corresponding isonitrile derivative being detected (^1H and ^{13}C NMR). In the case of the reaction of epoxides **1** and **2** some amount (see Table) of the corresponding 1,2-dicyano derivatives (compounds **9** and **10**) were also formed,respectively.[18] The opening reaction carried out with KCN in the same conditions, but in the absence of the metal salt catalyst, is completely uneffective (compare entries 15 and 19, Table). The reactions are completely *anti*-stereoselective, as shown by the reaction of epoxides **3**, **7** and **8** (entries 7, 8, 21, 22, and 24) in which only the *trans* isomer was detected. The reactions are also highly regioselective with the attack of the nucleophile on the less substituted carbon, except for styrene oxide (**6**) (entries 15 and 16, Table) in which a small but substantial attack of the nucleophile on the more substituted benzylic carbon occurs.



9 R= C_6H_{11}

10 R= CH_3

According to the previous hypotheses about the role of these metal salt catalysts in the above-mentioned aminolysis[16] and azidolysis[17] of epoxides, it appears that the effective catalysts in the present addition reactions of cyanide to epoxides are the metal ions, as a result of their ability to coordinate with the oxirane oxygen. It may be pointed out that the stereoselectivity and regioselectivity of the present metal salt-catalyzed cyanide addition to epoxides, and those of the previously studied aminolysis[16] and azidolysis[17] of the same epoxides exhibit strong analogies.

In conclusion, this new metal salt-catalyzed *anti*-stereoselective method for the cleavage of epoxides by cyanide affording selectively β-hydroxy nitriles appears to offer several advantages compared with other procedures reported in literature.[4-15] The reaction conditions are mild and the yields are quite fair, even when highly substituted epoxides are used. The cyanide is added to the epoxides directly as popular potassium cyanide avoiding the generation *in situ* of hydrogen cyanide in the direct addition, and the deprotection stage which is necessary when Me_3SiCN is used. The catalysts are quite common salts. Moreover, the use of a non-protic solvent (CH_3CN) allows this method to be utilized with protic-solvent sensitive substrates.

General Procedure and Identification of the β-Hydroxy Nitriles

A solution of the epoxide (5.0 mmol) in acetonitrile (5 ml) was treated with anhydrous metal salt (7.5 mmol) and KCN (7.5 mmol). The resulting reaction mixture was stirred at 70°C for the time shown in the Table, then cooled at room temperature, diluted with water and extracted with ether. Evaporation of the washed (water) ether extracts afforded a crude reaction mixture which was analyzed by GLC and ^1H NMR. β-Hydroxy nitriles were identified by comparison (^1H NMR and GLC) with authentic samples prepared in accordance with literature procedures.[4c,9,13,15] The structures of some previously unreported β-hydroxy nitriles (footnotes *p* and *s*, Table) were confirmed by satisfactory microanalysis results (C,H,N ± 0.3% of the calculated value) and by their ^1H NMR spectra (200 MHz, see Table).

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17. Chini,M.; Crotti,P.; Macchia,F. *Tetrahedron Lett.*, **1990**, *31*, 5641-5644.
18. *1-Hexyl-1,2-ethandicarbonitrile* (**9**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.94 (m,1H,$CHCN$), 2.73 (d,2H,J= 6.5 Hz, CH_2CN); ^{13}C NMR (200 MHz,$CDCl_3$) δ 119.7 and 116.5 (2 CN); MS 164 (M^+). *1-Methyl-1,2-ethandicarbonitrile* (**10**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.08 (m,1H, $CHCN$), 2.76 (d,2H,J= 6.3 Hz, CH_2CN); ^{13}C NMR (200 MHz, $CDCl_3$) δ 120.4 and 116.6 (2 CN); MS 94 (M^+).The obtained 1,2-dicyano derivatives **9** and **10** are not primary reaction products. Their formation is dependent on the reaction time, the amount of KCN, the type of metal salt, and the solvent. When the reaction of epoxides **1** and **2** is performed following the General Procedure (epoxide/KCN ratio 1:1.5), the amount of **9** (from **1**) and **10** (from **2**) is 12.0 and 5.5% respectively, after 18 h. Prolonged reaction time (20 h), and/or increased amount of KCN (epoxide/KCN ratio = 1:2), yielded increased amount of **9** (30%, reaction in CH_3CN, and 52%, reaction in THF, from **1**) and **10** (21%, reaction in CH_3CN, from **2**). Compounds corresponding to **9** and **10** were not detected in the reaction of the other epoxides examined. A complete rationalyzation of the formation of compounds **9** and **10** in these reactions is actually under investigation.
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