Pergamon

Tetrahedron Letters 40 (1999) 1041–1044

TETRAHEDRON LETTERS

Ring-Opening of Epoxyalcohols by Diethylaluminium Cyanide. Regio- and Stereoselective Synthesis of 1-Cyano-2,3-diols

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Received 15 October 1998; accepted 23 November 1998

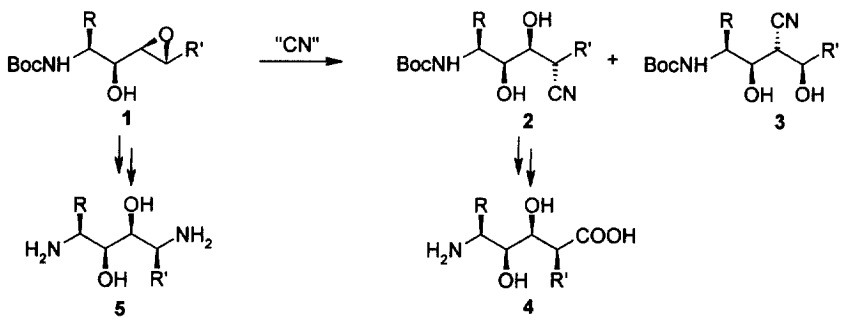
Abstract

Diethylaluminium cyanide is a highly selective reagent for the ring opening of 2,3-epoxyalcohols under mild conditions; the reaction takes place at C-3, with inversion of configuration, to give 1-cyano-2,3-diols.

Keywords: Aluminium and compounds; cyano compounds; epoxides; diols.

The ring-opening of epoxides by cyanide ion provides a convenient route to β-hydroxynitriles [1] and, through these, to β-hydroxyacids and the corresponding γ-lactones [2]; however, control of regioselectivity is not straightforward when the electrophilic positions of the oxirane ring are equally substituted. Thus, in an attempt to synthesize cyanodiols **2** from epoxides **1** (Scheme 1), we found that potassium cyanide in methanol or DMF gives mixtures of nitriles **2** and **3** in a ratio which is dependent upon the structure of R'. With bulky R' substituents, the reaction is sluggish and yields significant amounts of the undesired regioisomer **3**.

Scheme 1



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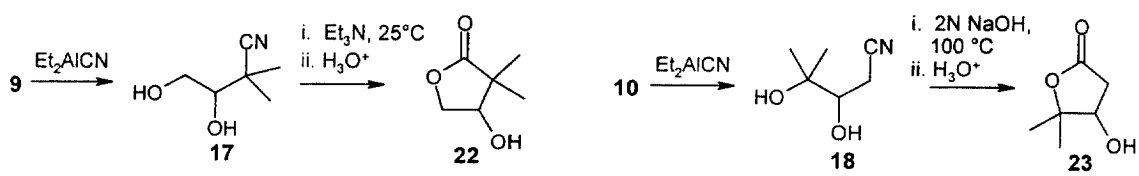
0040-4039/99/$ - see front matter
PII: S0040-4039(98)02520-9

It can be seen from the table that the reaction of 2,3-epoxyalcohols with diethylaluminium cyanide gives 3-cyano-1,2-diols in good yields and excellent regio- and stereoselectivity, irrespectively of the substitution pattern of the epoxide. While protection of the hydroxy group is not required, O-benzyl derivatives **6** and **8** behave similarly to the unprotected epoxyalcohols. The stereochemistry of the epoxide has no effect on the regioselectivity of the reaction; this is clearly demonstrated by comparison of the cis-epoxides **12** and **13** with the trans compounds **11**, **1a** and **1b**. The selectivity is very high even when the reaction involves attack at a quaternary or otherwise hindered carbon, such as in epoxides **9** and **1a**, respectively. The C-3 selectivity displayed by diethylaluminium cyanide is thus superior to that observed in the corresponding titanium-mediated ring-openings of epoxyalcohols [7]. A high preference for attack at C-3 has also been observed in the reaction of epoxyalcohols with diethylaluminium azide [20].

Ring-opening takes place with complete inversion of configuration, as demonstrated by the reaction of epoxides **1** and **11-13** in which only one isomer is formed, derived from *anti* attack by cyanide. This is true also for the cinnamyl epoxide **11** which gave partial *syn* attack in the reaction with diethylaluminium azide [20]. The last two entries in the table show that the methodology can be efficiently applied to the ring opening of homochiral epoxyalcohols. In this case (Scheme 1), ring-opening of the epoxide by diethylaluminium cyanide is the key step in a synthetic sequence in which four contiguous stereocenters have been established on an acyclic framework with complete control of the regio- and stereoselectivity.

The synthetic potential of the method is further demonstrated by the synthesis of β-hydroxylactones **22** and **23** (scheme 2) which are useful intermediates in the synthesis of natural products [21-23].

Scheme 2

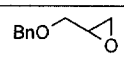
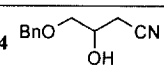
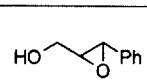
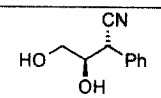
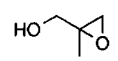
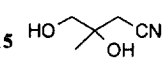
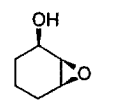
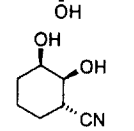
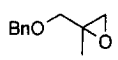
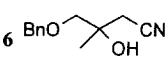
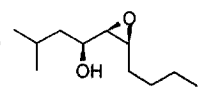
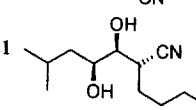
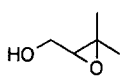
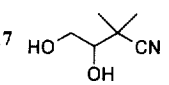
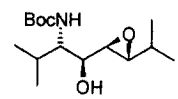
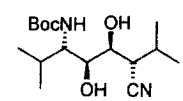
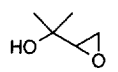
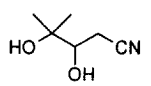
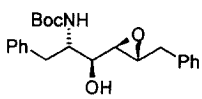
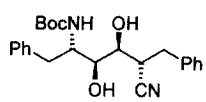


In the presence of a mild base, dihydroxynitrile **17**, obtained from the ring opening of epoxide **9** (Table 1) reacts smoothly to give a cyclic iminoether which is then hydrolyzed to the corresponding lactone **22**. Hydroxynitrile **18** (from epoxide **10**, Table 1) does not cyclize, but can be first hydrolyzed in aqueous base to a dihydroxyacid which then lactonizes to give **23**. By this route lactones **22** and **23** have been obtained in 54 and 65 % yield, respectively, from the corresponding epoxyalcohols **9** and **10**.

Cyanodiols **2** were pursued as intermediates for the synthesis of 2,3-dihydroxy-4-aminoacids **4**. Pseudopeptides based on non-hydrolyzable dipeptide isosteres such as **4** or the corresponding diaminodiols **5** are potent inhibitors of HIV-1 protease [3-5] and the epoxide route of scheme 1 appeared particularly attractive as it would offer access to both diaminodiol and dihydroxyaminoacid dipeptide isosteres **4** and **5** from the same intermediate **1** [6].

It is well known that the ring-opening of 2,3-epoxyalcohols can be selectively directed to the 3 position by Lewis acids coordinating to the oxygen atoms [7-9]. Diethylaluminium cyanide (Nagata's reagent [10,11]), a strong Lewis acid and cyanide donor, appeared thus a good candidate to perform the required transformation (**1→2**, Scheme 1). This reagent has been used in the cyanide fission of steroidal [10,11] and other epoxides [12-19] but its reactivity with epoxyalcohols [18,19] has never been investigated in a systematic way. Indeed, our expectations were fulfilled and treatment of epoxyalcohols **1** (R,R' = $CH(CH_3)_2$; R,R' = CH_2Ph) with Et_2AlCN gave cleanly the corresponding cyanodiols **2**.[1] In view of the potential synthetic interest of the reaction, this success encouraged us to extend the investigation to a wider and more general series of substrates: results are in Table 1.

Table 1.
Ring-opening of 2,3-epoxyalcohols by diethylaluminium cyanide.

Epoxyalcohol	Cyanodiol	% Yield[a]	C3:C2 Ratio[b]	Epoxyalcohol	Cyanodiol	% Yield[a]	C3:C2 Ratio[b]
6 	**14** 	94	93:7	**11** 	**19** 	85	94:6
7 	**15** 	38	>99:1	**12** 	**20** 	65	91:9
8 	**16** 	94	>99:1	**13** 	**21** 	74	>99:1
9 	**17** 	57	88:12	**1a**[c] 	**2a**[d] 	62	>99:1
10 	**18** 	72	>99:1	**1b**[c] 	**2b**[d] 	60	>99:1

[a] Isolated; not optimized. [b] Determined by 400 MHz ^{1}H NMR. [c] *S,S,R,R* stereoisomer. [d] *S,S,S,R* stereoisomer.

[1] General procedure. A 1M solution of Et_2AlCN in toluene (7.7 ml) is added via syringe, at 0 °C under an argon atmosphere, to a stirred solution of the epoxide (7 mmol) in dry toluene (10 ml). The reaction mixture is allowed to reach room temperature and stirring is continued until the reaction is judged to be complete by TLC (15 – 24 h). The solution is diluted with ethyl acetate (10 ml) and cooled to 0 °C. NaF (7.7 g) and water (1.0 ml) are added in the order, collecting the evolving gas (**CAUTION HCN is highly toxic**) into a basic aqueous solution. The resulting mixture is stirred at r.t. for 30 min, filtered through a pad of anhydrous sodium sulphate and evaporated to dryness. Flash chromatography of the residue (ethyl acetate/petroleum ether 1/1) gives the pure nitriles.

We have thus shown that 1-cyano-2,3-diols can be efficiently synthesized, under mild conditions, by the reaction of epoxyalcohols with diethylaluminium cyanide. Since epoxyalcohols are readily obtained in enantiomerically pure form by asymmetric epoxidation of allylic alcohols [24] and other methods [25], this methodology should find general application in the stereoselective synthesis of 2,3-dihydroxynitriles and the corresponding dihydroxyacids.

Acknowledgments

We thank the University of Trieste and *Istituto Superiore di Sanità* for financial support.

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