Pergamon

Tetrahedron Letters 39 (1998) 7971–7974

TETRAHEDRON LETTERS

Regio- and Stereoselective Ring Opening of 2,3-Epoxyalcohols with Diethylaluminium Azide

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Received 24 June 1998; accepted 18 August 1998

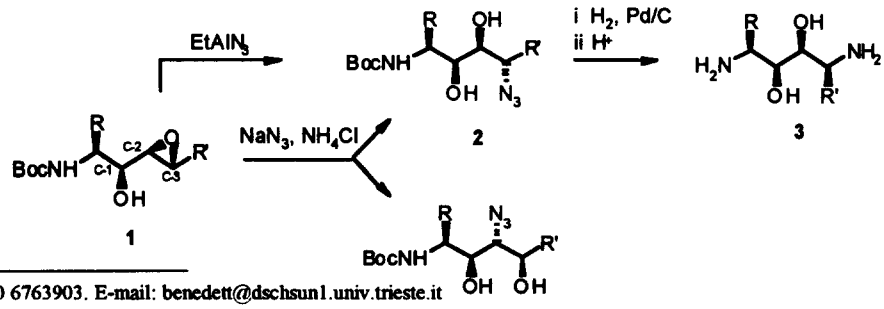
Abstract

2,3-Epoxyalcohols react with diethylaluminium azide under mild conditions to give 3-azido-1,2-diols resulting from the regio- and stereoselective attack of the nucleophile at the epoxide C-3. The high regioselectivity (>25:1) observed with both *cis* and *trans* substituted epoxides is not affected by bulky substituents at C-3. The method has been successfully applied also to the synthesis of diaminodiol dipeptide isosteres.

Keywords: Aluminium and compounds; Azides; Epoxides; Isosteres

The 3-amino-1,2-diol structure is present in several classes of biologically active compounds, such as, for example, β-blocker drugs [1,2], anti-hypertensive renin inhibitors [3,4] and aminosugars [5]. 3-Amino-1,2-diols are also valuable intermediates in the synthesis of a variety of other bioactive molecules, including α-aminoacids [6], α-hydroxy-β-aminoacids [7,8] and dipeptide isosteres [9,10]. A convenient approach to this structure is represented by the ring- opening of readily available 2,3-epoxyalcohols by ammonia or azide [11]. Recently we have followed this approach in the synthesis of a series of C_2-symmetric and pseudo-symmetric dihydroxyethylene dipeptide isosteres **3** with all-*S* configuration [10] (Scheme 1).

Scheme 1



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0040-4039/98/$ - see front matter
PII: S0040-4039(98)01733-X

In the course of that work we found that ring opening of epoxides **1** with NaN_3 and NH_4Cl takes place selectively at the C-3 position to give the desired azidodiols **2** when R'= CH_2Ph or R'=CH_2c-Hex. However, when R' is the bulkier isopropyl group, the reaction is sluggish and yields a mixture of C-2 and C-3 regioisomers. Trimethylsilyl azide, in the presence of catalytic titanium tetraisopropoxide [12] also failed to afford the required product **2** (Scheme 1, R,R'=isopropyl), leading instead to the loss of the Boc protecting group. We thus turned to aluminium reagents whose ability to promote the nucleophilic ring opening of oxiranes is well established [13,14]; our initial attempt with trimethylsilyl azide and diethylaluminium chloride was not successful as this reagent gave a mixture of azido-alcohols and chlorohydrins [15]. Eventually the desired azidodiol **2** (R,R' = isopropyl) was obtained by the reaction of epoxide **1** with diethylaluminium azide (Scheme 1). This reagent was prepared and studied in the 60's [16,17], but it has been seldom used in organic synthesis [18,19]. In particular there appears to be only one report on the ring-opening of epoxides with Et_2AlN_3 [18], while, to the best of our knowledge, the use of this reagent in the cleavage of epoxyalcohols has never been reported. This prompted us to extend the investigation to a representative series of 2,3-epoxyalcohols; results are in the Table.

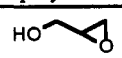
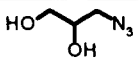
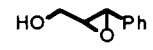
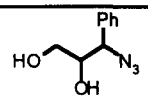
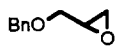
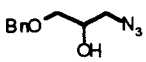
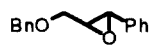
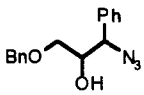
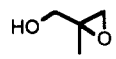
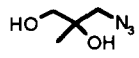
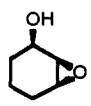
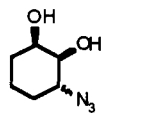
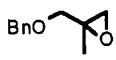
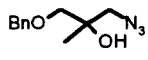
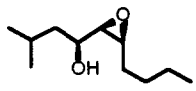
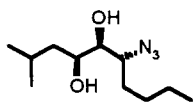
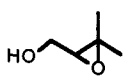
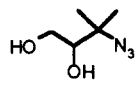
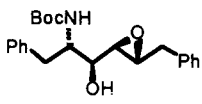
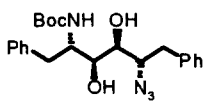
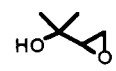
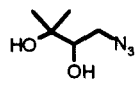
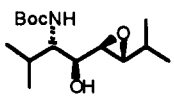
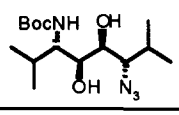
Treatment of 2,3-epoxyalcohols with diethylaluminium azide, prepared *in situ* from sodium azide and diethylaluminium chloride [15] gave the corresponding 3-azido-1,2-diols in good yields[1] (Table 1). The main by-products are the corresponding 3-chloro-1,2-diols which were identified from the ^1H and ^{13}C NMR spectra of the crude reaction mixtures and by comparison with the spectra of authentic samples obtained from the reaction of epoxyalcohols with diethylaluminium chloride. Regioisomeric 2-azido-1,3-diols were not detected by NMR and thus a regioselectivity higher than 25:1 can safely be assumed. As can be seen from the Table (entries 2, 4 and 8) protection of the hydroxy group as a benzyl ether does not affect the reactivity or the regioselectivity.

The very high C-3 selectivity displayed by diethylaluminium azide is not affected by substitution at the 3 position (entries 5, 7-12). Cyclic (*cis*-constrained) and acyclic *cis*-2,3-epoxyalcohols (entries 9, 10), when treated with this reagent, also gave the corresponding 3-azido-1,2-diols. The structures of these products were confirmed by comparison with literature data [12] (entry 9) or by the ^1H NMR analysis (400 MHz, $CDCl_3$) of the azidodiol and its di-trifluoroacetate (entry 10). Diethylaluminium azide is thus superior, in this respect, to titanium reagents whose C-3 selectivity is hampered by *cis*-substitution and by steric hindrance at the C-3 position [1].

[1] Typical procedure. A 1.8M solution of diethylaluminium chloride in toluene (13.6 mmol) is added via syringe, under an argon atmosphere, to a well stirred suspension of sodium azide (15 mmol) in dry toluene and the resulting mixture is stirred for 4 h at 20 °C. The mixture is cooled to –78 °C and a solution of the epoxide (6.8 mmol) in 5 ml toluene is added dropwise. The reaction mixture is stirred for 1 h at –78 °C and for 16 h at 25 °C, then cooled to 5 °C and diluted with 30 ml ethyl acetate. Sodium fluoride (13 g) and water (1.8 ml) are added and the resulting suspension is stirred for 0.5 h at room temp. Filtration through a short pad of anhydrous sodium sulphate and solvent evaporation gives the crude product which is purified by column chromatography or crystallization.

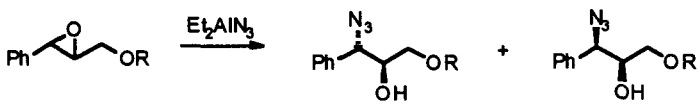
Table 1

Ring Opening of 2,3-Epoxyalcohols by Diethylaluminium Azide.[a]

Entry	Epoxyalcohol	Azidodiol	%Yield	Entry	Epoxyalcohol	Azidodiol	%Yield
1			38	7			74[b,c]
2			68[b]	8			65[b,c]
3			89	9[d]			83
4			69[b]	10[d]			84
5			69[b]	11			77
6			62[b]	12			79

[a] Yields refer to isolated products and are not optimized.
[b] 3-Chloro-1,2-diol is the main by-product.
[c] Mixture of *threo* and *erythro* diastereoisomers.
[d] Racemic mixture.

Scheme 2



4a R = H
4b R = Bn

5a : **6a** 7 : 3
5b : **6b** 5 : 1

Ring-opening of 3-substituted 2,3-epoxyalcohols (entries 7-12) is highly stereoselective, leading to the formation of the corresponding azidodiols with inversion of configuration at C_3, with the exception of the phenyl substituted epoxides **4** (Scheme 2). In this case we obtained a mixture of diastereoisomers **5** and **6** from *anti* and *syn* attack. A similar behaviour has been observed in the reaction of the same epoxide with trimethylsilyl azide in the presence of catalytic $Ti(O\text{-}iPr)_4$; the formation of the *syn* product **6** can be attributed either to an intramolecular attack by an azide-containing metal species co-ordinated to the epoxide oxygen or to an S_N1 reaction at the benzylic center, following ring opening of the epoxide promoted by co-ordination of the Lewis acid [12, 20]. It is noteworthy that the corresponding chlorodiol,

which is a byproduct of the reaction, is also formed as a mixture of diastereoisomers in a similar ratio.

Finally, entries 11 and 12 show that this methodology can be efficiently applied to the ring-opening of highly substituted, homochiral epoxy alcohols leading, in this case, to 3-azido-1,2-diols in which four contiguous chiral centers have been established in a stereocontrolled way [10]. Catalytic hydrogenation of the azides over palladium and deprotection (Scheme 1) gave the corresponding, enantiomerically pure, C-2 symmetric diaminodiols **3** (R,R'=CH_2Ph; $CH(CH_3)_2$), thus unambiguously confirming the regio- and stereochemical features of the Et_2AlN_3 promoted ring opening.

We have thus demonstrated that diethylaluminium azide is a mild and efficient reagent for the regio- and stereoselective ring opening of epoxyalcohols; as the C-3 selectivity is not affected by *cis* or hindered substituents, this method should find general application in the synthesis of 3-amino-1,2-diols.

Acknowledgements

This work was supported by MURST (60%) and, in part, by Istituto Superiore di Sanità (ISS).

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