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A New Efficient Way To α,ω-Diaminoitols By Direct Azidation Of Unprotected Itols.

V. Glaçon, A.El Meslouti, R.Uzan, G.Demailly, D.Beaupère*

Laboratoire de Chimie Organique, Université de Picardie Jules Verne, 33 rue St-Leu F-80039 Amiens (Fr.).

Abstract :Unprotected pentitols and erythritol are transformed into α,ω-diazido derivatives by successive treatment with thionyl chloride and sodium azide. Reduction by catalytic hydrogen transfer gives the α,ω−diaminoitols.

Diaminoitols can be used as precursors of polyamides[1] and chelating agents[2] and are important in medicinal chemistry.[3]

Direct amination of sugars by either ammonia or an amine readily takes place at the anomeric position but not at other sites on the sugar ring.[4] Substitution of an amino function at a non-anomeric site generally involves nucleophilic displacement of sulfonates[5] or ring opening of anhydro derivatives[6] with azide ions followed by reduction.

Multisteps syntheses of 3,4-disubstituted α,ω-diazidomannitol have been reported *via* bis-sulfonates[7] and, more recently, *via* bis-epoxides[8] in less than 40 and 50% yields respectively.

O-Cyclic sulfite group was used to introduce an azido group both regio and stereoselectively.[9] Moreover we have shown recently that a cyclic sulfite group could be used in a "one pot" synthesis of a glycosyl azide from either partially protected or unprotected monosaccharides.[10]

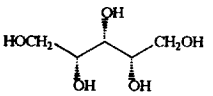
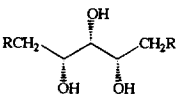
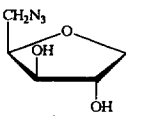
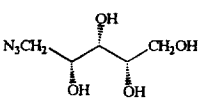
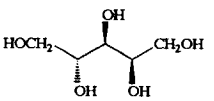
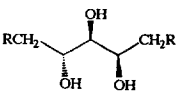
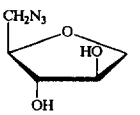
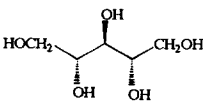
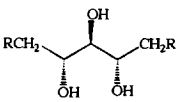
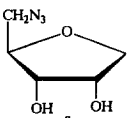
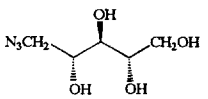
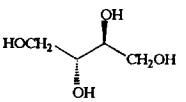
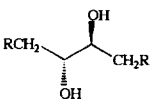
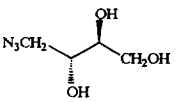
To our knowledge, direct access to α,ω-diaminoitols without any previous protection has never been reported. Therefore, we studied the derivatisation of unprotected itols[11] and our results concerning the functionalisation of monosaccharides without any protection prompted us to apply the same method to several itols.

Herein we report a new preparation of α,ω-diaminopentitols and erythritol involving cyclic sulfites and α,ω-diazidoitols as intermediates.

$$HOCH_2\text{-}(CHOH)_n\text{-}CH_2OH \xrightarrow[2)\ NaN_3]{1)\ SOCl_2} N_3CH_2\text{-}(CHOH)_n\text{-}CH_2N_3 \xrightarrow[Pd/C]{HCOONH_4} H_2NCH_2\text{-}(CHOH)_n\text{-}CH_2NH_2$$

A suspension of the itol (1g) in CH_2Cl_2 (50mL) was stirred with thionyl chloride ($SOCl_2$, 3eq.) and pyridine (6eq.) for 40 mn. at -30°C. The reaction mixture was filtered and solvent removed to give a yellow syrup. This latter reacted with sodium azide (NaN_3, 6eq.) in DMF at 130°C for two hours. After evaporation of DMF and liquid column chromatography on silicagel (AcOEt-MeOH) the α,ω-diazido compound was obtained as the main product. In the Table, we report the results for three pentitols and the erythritol. The yields were not increased when the crude products were acetylated before purification by chromatography.

Table. Azidation of pentitols and erythritol

Substrates	Isolated products (Yield in %)		
 **1** xylitol	 **2** R=N_3 (72) **15** R=NH_2 (82)	 **3**[a] (11)	 **4**[a] (10)
 **5** D-arabinitol	 **6** R=N_3 (55) **16** R=NH_2 (72)	 **7** (15)	
 **8** ribitol	 **9** R=N_3 (50) **17** R=NH_2 (75)	 **10**[a] (13)	 **11**[a] (10)
 **12** erythritol	 **13** R=N_3 (80) **18** R=NH_2 (71)		 **14**[a] (traces)

a / inseparable mixture of isomers.

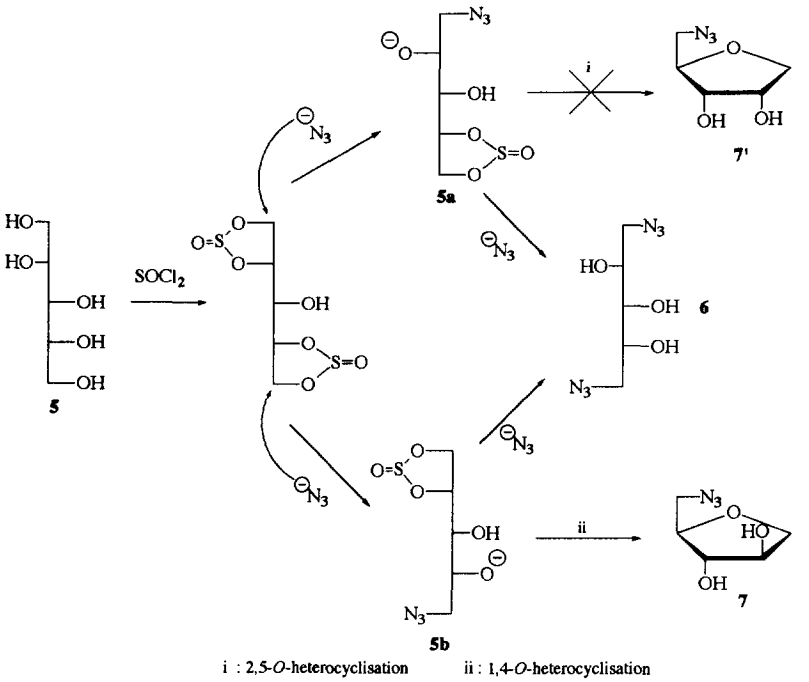
To explain the formation of azido compounds, we analyzed the yellow syrup obtained after treatment with $SOCl_2$. Bis-*O*-sulfinyl derivatives of ribitol and D-arabinitol were very unstable, however the sulfinyl precursors of **2** and **13**, namely 1,2:4,5-di-*O*-sulfinyl xylitol and 1,2:3,4-di-*O*-sulfinyl erythritol, respectively, were isolated. These intermediates were identified by ^{13}C NMR spectroscopy.[12] A nucleophilic attack by two azide ions at both primary carbons of the bis-*O*-sulfinyl intermediates led to the α,ω-diazidoitols.

Attack of azide at the primary carbon atom led to the monoazido compounds **4**,**11**, **14** or to the anhydro compounds **3**,**7**,**10** by a further intramolecular heterocyclisation.

In the same experimental conditions, no acyclic monoazido derivative was observed with D-arabinitol ; only the compound **7** resulting from 1,4-*O*-heterocyclisation was isolated as by product.[13] This selectivity, also

observed for halogenation of itols[11b], can be explained by the following mechanism (Scheme). The first attack occurred at C-1 or C-5 leading respectively to **5a** or **5b**. The 2,5-*O*-intramolecular heterocyclisation of **5a** to give **7'**, is unfavorable due to the OH-2, OH-3 eclipsed conformation, hence only the anhydro compound **7** is obtained.

Scheme



In the case of erythritol, we have shown that the formation of monoazido derivative **14** could be favored when the addition of NaN_3 was performed at room temperature, the 1-azido-1-deoxy erythritol **14** being isolated in 60% yield.

α,ω-Diaminoitols were obtained by catalytic hydrogen transfer from ammonium formate to the corresponding α,ω-diazido compounds. Thus diazidoitol (1g) in MeOH (50 mL) was treated with ammonium formate (1,56g.) and Pd-C (1,76g) at 60°C for 5 mn. After removal of the catalyst by filtration and solvent evaporation, α,ω-diaminoitol was obtained as the sole product ; yields are reported in the Table. When reduction was performed on peracetylated diazidoitols, acetyl group migration occurred in each case to give the respective di-acetamido derivatives.

Recently, vicinal diamines have been synthesized from non carbohydrate diols by opening cyclic sulfates derivatives with secondary amines.[14] The different reactivity of cyclic sulfates, as compared to sulfites is due to a resulting alkyl sulfate leaving group after the initial ring opening. This particular behavior of cyclic sulfates can be used to explain why the reaction was limited to secondary amines, and why primary amines lead to aziridines.[14]

All azido and amino compounds were characterized by ^{13}C NMR spectroscopy[15] and comparison with authentic compounds synthesized by an alternative route involving α,ω-dihalogenated itols.[16]

In summary, we proposed a direct "one pot " access to α,ω-diazidoitols from unprotected itols *via* the formation of bis-*O*-cyclic sulfites. The following reduction of diazidoitols by catalytic hydrogen transfer with ammonium formate as hydrogen donnor led to the corresponding α,ω-diaminoitols. The same procedure is currently in use to extend this chemistry to new systems.

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12 By ^{13}C NMR spectroscopy in $CDCl_3$ chlorinated itols are not detected and cyclic sulfites are characterized by primary carbon : $68 < \delta_{ppm} < 70$. For an example 1,2:3,4-di-*O*-sulfinyl-erythritol was isolated as a mixture of 4 stereoisomers (endo/exo). ^{13}C NMR data in $CDCl_3$: δppm from TMS 68.6, 69.1, 70.2 (C-1, C-4); 77.7, 79.2, 79.6 (C-2, C-3).

13 ^1H NMR data in $CDCl_3$ for acetylated compound **7** : δppm from TMS 5.11 (m, $J_{2,3}$=0.4Hz, H-2) ; 4.95 (dd, $J_{3,4}$=3.5Hz, H-3) ; 3.96 (d,J=2.7Hz, H-1a, H-1b) ; 3.87 (ddd, $J_{4,5}$=3.5Hz, H-4) ; 3.52 (dd, $J_{4,5a}$=5.9Hz, H-5a); 3.37 (dd, J_{5a-5b}=13.1Hz, H-5b) ; 2.02 (CH_3 acetates).

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15 Selected ^{13}C NMR data δ_{ppm} from TMS in CD_3OD. **2** : 54.5 (C-1, C-5) ; 73.2 (C-2, C-4) ; 73.8 (C-3) ; **15** : 46.0 (C-1, C-5) ; 74.6 (C-2, C-4) ; 75.3 (C-3).

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