Pergamon

Tetrahedron Letters 41 (2000) 5053–5056

TETRAHEDRON LETTERS

Heterocyclisation of free or partially protected alditols via their bis-cyclic sulfate derivatives. Versatile synthesis of aza and thiodeoxyanhydroalditol with *erythro*, *threo*, *arabino*, *gulo*, *talo* or *manno* configuration

Virginie Glaçon, Mohammed Benazza,* Daniel Beaupère and Gilles Demailly*

Laboratoire de Chimie Organique, Université de Picardie Jules Verne, 33 rue Saint-Leu, F-80039 Amiens, France

Received 18 April 2000; accepted 12 May 2000

Abstract

The bis-cyclic sulfate derivatives of erythritol (**1**), D,L-threitol (**5**), 3,4-di-*O*-benzyl-D-mannitol (**9**), 1,2-*O*-isopropylidene-D-mannitol (**14**) and 1-*O*-benzyl-D,L-xylitol (**18**) were submitted to nucleophilic attack by allylamine or sodium sulfide. In both cases, heterocyclisation occurred and aza or thioanhydrodeoxy-alditols were obtained in moderate to good yields (40 to 89%). With compound **9**, 1,5-anhydro-5-thio-L-gulitol (**12**) was obtained as the main product, a result that is in contrast with previous results reported in the literature using bis-epoxide as bielectrophile intermediate.[1] © 2000 Published by Elsevier Science Ltd.

Keywords: alditol; bis-cyclic sulfates; heterocyclisation; thiosugar; azasugar.

The potential activity of azasugars as glycosidase inhibitors[2] has aroused much interest among organic chemists in recent years.[3] The development of synthetic methods for azaheterocycles such as hydroxylated pyrrolidines, piperidines or azepanes has been described in several papers.[4] In addition to cyclic sugars as glucidic substrates,[5] alditols such as D-mannitol and the pentitols have proved to be excellent precursors for heterocycles containing not only nitrogen, but also sulfur, selenium and phosphorus.[1,6] Among bielectrophile intermediates developed in the literature we outlined the bis-epoxides,[7] the bis-aziridines,[8] the dihalogenated[9] and the disulfonates derivatives.[4b,6c]

As part of our programme on the development of alditol chemistry, we have first attempted the synthesis of aza and thioanhydroalditols compounds from bis-cyclic sulfites of hexitols and pentitols prepared in the laboratory from the corresponding free alditols. The result obtained is the hydrolysis of cyclic sulfites resulting from attack on the sulfur atom.

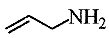
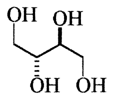
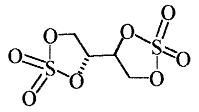
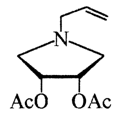
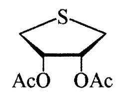
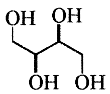
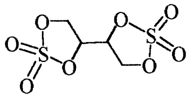
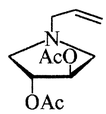
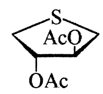
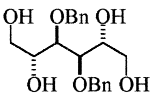
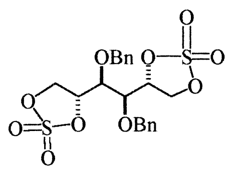
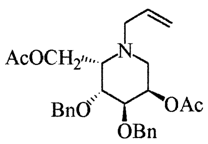
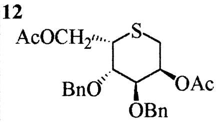
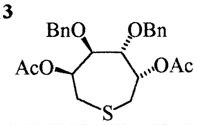
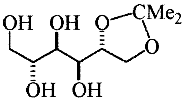
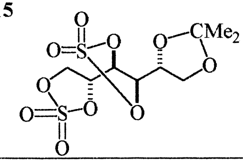
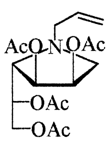
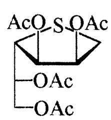
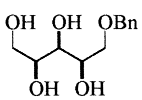
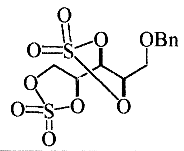
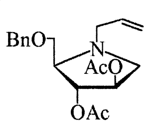
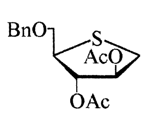
* Corresponding authors. Fax +33(3)22827562; e-mail: mohammed.benazza@sc.u-picardie.fr

PII: S0040-4039(00)00791-7

In the present note we report the synthesis of aza and thioheterocycles via the vicinals 1,2:3,4 and 1,2:5,6-bis-cyclic sulfates derivatives of some alditols. The substrates studied were erythritol (**1**), D,L-threitol (**5**), 3,4-di-*O*-benzyl-D-mannitol (**9**), 1,2-*O*-isopropylidene-D-mannitol (**14**) and 1-*O*-benzyl-D,L-xylitol (**18**).

Compounds **1**, **5**, **9**, **14** and **18**[10] indicated above were first transformed into their mixtures of diastereoisomeric cyclic di-*O*-sulfinyl derivatives in very good yields by the reaction with *N*,*N*′-diimidazole thionyl ($SOIm_2$) in THF at low temperature. Subsequent oxidation by $NaIO_4$ and a catalytic amount of $RuCl_3$[11] led to di-*O*-sulfenyl derivatives in yields better than 90% based on the free or partially protected starting alditol. In each case, we obtained only one regioselective isomeric di-*O*-sulfenyl derivative (see Table 1). If with D-mannitol **10** and **15**, the vicinal positions 1,2:5,6 and 3,4:5,6, respectively, of the two cyclic sulfate groups were easily proved by NMR

Table 1
Regioselective heterocyclisation of some 1,2:3,4 and 1,2:5,6-bis-cyclic sulfate derivatives of alditols using sodium sulfide or allylamine as nucleophilic reagents

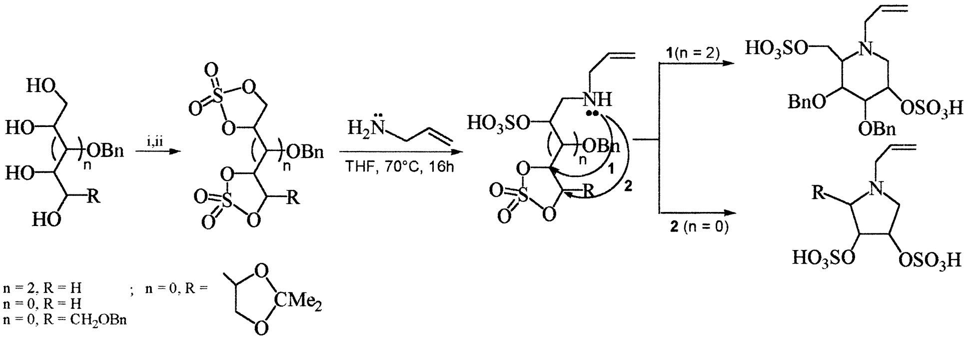
				Na_2S, $9H_2O$	
Substrats	Suggested cyclic sulfate derivatives**	Azaheterocyclic derivatives	Yield(%)*	Thioheterocyclic derivatives	Yield(%)*
 Erythritol (**1**)	**2** 	**3** 	50	**4** 	80
 D,L-threitol (**5**)	**6** 	**7** 	65	**8** 	89
 3,4-Di-*O*-benzyl-D-mannitol (**9**)	**10** 	**11** 	40	**12**  **13** 	55 22
 1,2-*O*-isopropylidene-D-mannitol (**14**)	**15** 	**16** 	40	**17** 	50
 1-*O*-benzyl-D,L-xylitol (**18**)	**19** 	**20** 	55	**21** 	40

*Isolated yields from bis-cyclic sulfate derivatives; **Obtained by oxidation of corresponding bis-cyclic sulfite derivatives in > 90% yields from the corresponding alditol derivatives.

spectroscopy, this was not the case for the other bis-cyclic sulfates **2**, **6** and **19**. Indeed, in the case of compound **10**, the presence of benzyl groups in positions 3 and 4, together with the plane and zigzag structure of D-mannitol should favour vicinal cyclic sulfates. In the case of compound **15**, the coupling constant of $J_{3,4} = 0$ Hz excluded the 3,5:4,6-bis-cyclic sulfate structure and favoured the 3,4:5,6-di-*O*-sulfenyl derivative. With the rest of the cases we suggest that it is the vicinal bis-cyclic sulfates, which could be easily formed.

The previously obtained crystallised bis-cyclic sulfates were first treated with allylamine in THF as solvent at 70°C overnight. Acid hydrolysis of the acyclic sulfates, followed by acetylation led to the results shown in Table 1. Note that in all cases we observed spontaneous heterocyclisation without added base as described by van Boom and co-workers with monocyclic sulfate derivatives.[6b] The *N*-allylpyrolidines **3** (*erythro*), **7** (D,L-*threo*), **16** (D-*talo*), **20** (D,L-*arabino*) and the *N*-allylpiperidine **11** (L-*gulo*) gave yields of 40 to 65%.

This heterocycle formation suggests an initial and systematic opening of the cyclic sulfate at the primary position followed by an azacyclisation involving regioselective opening of the second cyclic sulfate (see Scheme 1). Compounds **11**, **16** and **20** are obtained by regioselective azaheterocyclisation with configuration inversion of the involved secondary carbon atom in the corresponding substrates.



Scheme 1. (i) $SOIm_2$, THF, –10°C, 30 min; (ii) $NaIO_4$, $RuCl_3$, $H_2CCl_2/CH_3CN/H_2O$

With the 3,4-di-*O*-benzyl-1,2:5,6-di-*O*-sulfenyl-D-mannitol (**10**), heterocyclisation is mainly 1,5 directed with inversion of the configuration at C-5. The low yield observed (40%) could be attributed to the presence of the allylamine group, which is sensitive to the sulfate hydrolysis conditions (aqueous H_2SO_4 under heating).

Due to these interesting results thioheterocyclisation was attempted using sulfide ion ($S^{=}$). In the case of the tetritols, 1,4-primary–primary heterocyclisation appears to take place readily in good yields (Table 1); the derivatives 1,4-thio-dideoxyanhydroerythritol (**4**) and D,L-threitol (**8**) were obtained in 80 and 89% yields, respectively. On the other hand, with compounds **15** and **19**, primary–secondary cyclisation appears to occur less readily in moderate yields (50 and 40%, respectively). For a derivative of D-mannitol **10**, there is competition between 1,5 heterocyclisation leading to the derivative 2,3,4,6-tetra-*O*-acetyl-1,5-thio-dideoxy-L-gulitol (**12**) as the main product (55%). The thiepane derivative **13** was isolated as a by-product in a yield of 22% after acetylation. This result is of interest in comparison with the heterocyclisation carried out with the bis-epoxide derivative; in this latter case it is the thiepane which is produced in the major part.[1]

In conclusion, we have developed efficient synthetic methods for 5-, 6- and 7-aza and thio-dideoxyheterocycles with the use of bis-cyclic sulfates as bielectrophile intermediates. Work is in progress to exploit this methodology in the synthesis of other heterocycles and of cyclitols.

Acknowledgements

The authors thank the Conseil Régional de Picardie for its financial support.

References

1. Le Merrer, Y.; Fuzier, M.; Dosbaa, I.; Foglietti, M. J.; Depezay, J. C. *Tetrahedron* **1997**, *53*, 16731–16746.
2. (a) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199–210; (b) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340–347; (c) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors*; Wiley-VCH, Eds.: Weinheim, 1999; (d) McCort, I.; Fort, S.; Duréault, A.; Depezay, J. C. *Bioorg. Med. Chem.* **2000**, *8*, 135–143.
3. (a) Thomassigny, C.; Bennis, K.; Gelas, K. S. *Synthesis* **1997**, *2*, 191–194; (b) Pakulski, Z. *Polish J. Chem.* **1996**, *70*, 667–670; (c) Matos, C. R. R.; Lopes, R. S. C.; Lopes, C. C. *Synthesis* **1999**, *4*, 571–573.
4. (a) Nishimura, Y.; Shitara, E.; Takeuchi, T. *Tetrahedron Lett.* **1999**, *40*, 2351–2354; (b) Esposito, A.; Falorni, M.; Taddei, M. *Tetrahedron Lett.* **1998**, *39*, 6543–6546; (c) Zhou, P.; Salleh, H. M.; Chan, P. C. M.; Lajoie, G.; Honek, F.; Nambiar, P. T. C.; Ward, O. P. *Carbohydr. Res.* **1993**, *239*, 155–166; (d) Duréault, A.; Tranchepain, I.; Depezay, J. C. *J. Org. Chem.* **1989**, *54*, 5324–5330.
5. (a) Marek, D.; Wadouachi, A.; Beaupère, D. *Synthesis* **1999**, *5*, 839–843; (b) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1999**, *40*, 9375–9378; (c) Furneaux, R. H.; Lynch, G. P.; Way, G.; Winchester, B. *Tetrahedron Lett.* **1993**, *34*, 3477–3480; (d) Baxter, E. W.; Reitz, A. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1419–1422.
6. (a) Yan, Y. Y.; Rajunbabu, T. V. *J. Org. Chem.* **2000**, *65*, 900–906; (b) van Der Klein, P. A. M.; Filmon, W.; Broxterman, H. J. G., van Der Marel, G. A.; van Boom, J. H. *Synthetic Commun.* **1992**, *22*, 1763–1771; (c) Duréault, A.; Portal, M.; Depezay, J. C. *Synlett* **1991**, 225–226; (d) Holz, J.; Heller, D.; Stürner, R.; Börner, A. *Tetrahedron Lett.* **1999**, *40*, 7059–7062.
7. (a) Le Merrer, Y.; Gravier, C.; Maton, W.; Numa, M.; Depezay, J. C. *Synlett* **1999**, 1322–1324; (b) Lohray, B. B.; Jayamma, Y.; Chatterjee, M. *J. Org. Chem.* **1995**, *60*, 5958–5960; (c) Qian, X.; Varas, F. M.; Wong, C. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1117–1122.
8. McCort, I.; Duréault, A.; Depezay, J. C. *Tetrahedron Lett.* **1998**, *39*, 4463–4466.
9. (a) Kim, B. M.; Bae, S. J.; Seomoon, G. *Tetrahedron Lett.* **1998**, *39*, 6921–6922; (b) Lundt, I.; Madsen, R. *Synthesis* **1993**, *7*, 714–720.
10. Crombez, C.; Benazza, M.; Fréchou, C.; Demailly, G. *Carbohydr. Res.* **1998**, *307*, 355–359.
11. Gao, Y.; Sharpless, K. B. *J. Am.Chem. Soc.* **1988**, *110*, 7538–7539.