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# New synthesis of alditol thiaheterocycles via ring closure of vicinal bis-cyclic thionocarbonates of alditols

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**Abstract**—A new thiaheterocyclisation of alditols involving bis-cyclic thionocarbonate derivatives as bielectrophilic intermediates is reported. The polyhydroxylated tetrahydrothiophene, tetrahydropyrane and thiepane rings from erythritol, D,L-threitol, D-arabinitol, D-mannitol and galactitol were efficiently obtained. 

One of the most important routes to polyhydroxylated thioheterocycles is the thiaheterocyclisation of bielectrophilic alditols such as bis-epoxides,[1] bis-halogenated derivatives,[2] bis-sulfonates[3] and, more recently, bis-cyclic sulfates[4] in the presence of sulphide ion ($S^{=}$).

Thus, the 1,2:3,4 and 1,2:5,6 bis-cyclic sulphates of alditols (from erythritol, D,L-threitol, 3,4-di-*O*-benzyl and 1,2-*O*-isopropylidene-D-mannitol, and 1-*O*-benzyl-D,L-xylitol) undergo thiaheterocyclisation in good yields.[4] Unfortunately, this type of intermediate, obtained by oxidation of the corresponding cyclic sulphites, is limited to alditols with only four free alcohol functional groups as substrates. Bis-cyclic sulphites of alditols are readily obtained directly from free alditols but undergo hydrolysis under thiaheterocyclisation conditions ($Na_2S{\cdot}9H_2O$ in acetone–$H_2O$ or DMSO). Apart from bis-cyclic sulphites, cyclic thionocarbonates obtained from vicinal diols interested us for their use in organic synthesis, where they are useful both as protecting groups and as precursors of olefins,[5] azides,[6] thioethers[6] and iodates.[7] Also, they can rearrange to give cyclic thiolcarbonates,[6,8] undergo reduction[9] and be readily transformed into cyclic carbonates by reaction with tin reagents such as *n*-dibutyltin oxide (*n*-$Bu_2SnO$) or bis-*n*-tributyltin oxide ($((n\text{-}Bu_3Sn)_2O)$).[10] However, no heterocyclisation via bis-cyclic thionocarbonates has been reported in the literature.

In the present communication, we report a new application of cyclic thionocarbonates which is the thiaheterocyclisation of vicinal bis-cyclic thionocarbonates of alditols by reaction with sodium sulphide in DMSO. The bis-cyclic thionocarbonates are obtained in good yield by treatment of the stannylene acetal complexes of erythritol, D,L-threitol, xylitol, ribitol, D-arabinitol, D-mannitol and galactitol by the phenylthionochloroformate reagent, PhOC(S)Cl.[11]

The first thiaheterocyclisation attempted were carried out on the 1,2:3,4-bis-cyclic thionocarbonates of tetritols **1** and **4** by reaction with $Na_2S{\cdot}9H_2O$ under the thiaheterocyclisation conditions of α,ω-dibromoalditols (rt, ~15 min, DMSO)[2a] (Table 1, entries 1 and 2). The desired tetrahydrothiophenes **3** (*erythro*) and **6** (*threo*), were obtained in reasonable yields after acetylation (50 and 63% isolated yields, respectively). A similar reaction involving xylitol 1,2:4,5-bis-cyclic thionocarbonate (**8**; R = H, Scheme 1), which is the first example of a bis-cyclic thionocarbonate of a pentitol, yielded after acetylation, an inseparable mixture of the two compounds **9** (tetrahydrothiopyrane) and **10** (tetrahydrothiophene) (entry 3), in 50% total yield and in 1/4 ratio (determined by $^{13}C$ NMR spectroscopy). The formation of these two compounds can be explained by an initial regioselective attack by the $S^{=}$ ion on the primary site C-1 (=C-5) leading to the thiolate intermediate **8a**. Two cyclisations can then occur in which 6-*endo*-*tet* (**9a**, R = H, path a) competes with 5-*exo*-*tet* followed by inversion of the configuration of C-4 (**10a**, R = H, path b). The latter was the preferred pathway. In contrast, the thiaheterocyclisation carried out on the 3-*O*-acetyl-bis-cyclic thionocarbonate derivative of xylitol **11** (entry 3) led mainly to 6-*endo*-*tet* heterocyclisa-

*Keywords*: alditol; bis-cyclic thionocarbonate; thioheterocycle; thiepane; thiophene; thiopyrane.

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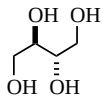
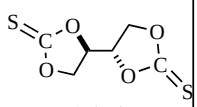
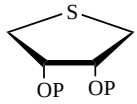
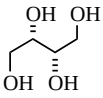
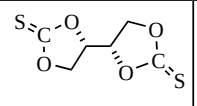
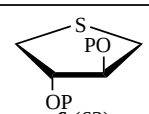
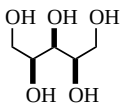
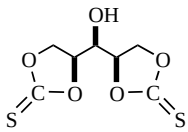
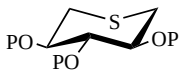
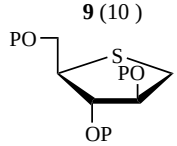
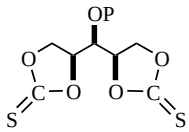
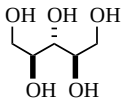
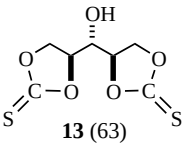
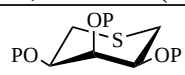
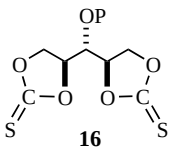
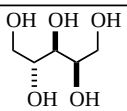
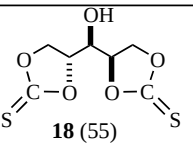
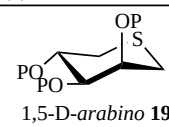
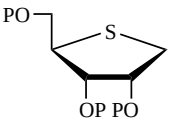
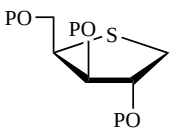
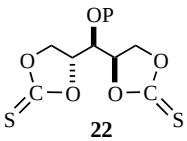
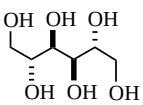
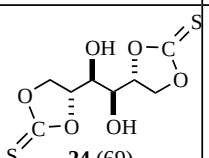
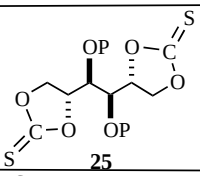
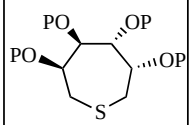
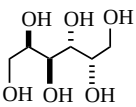
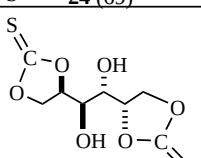
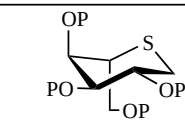
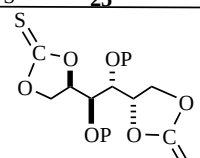
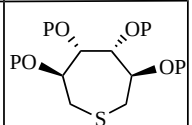
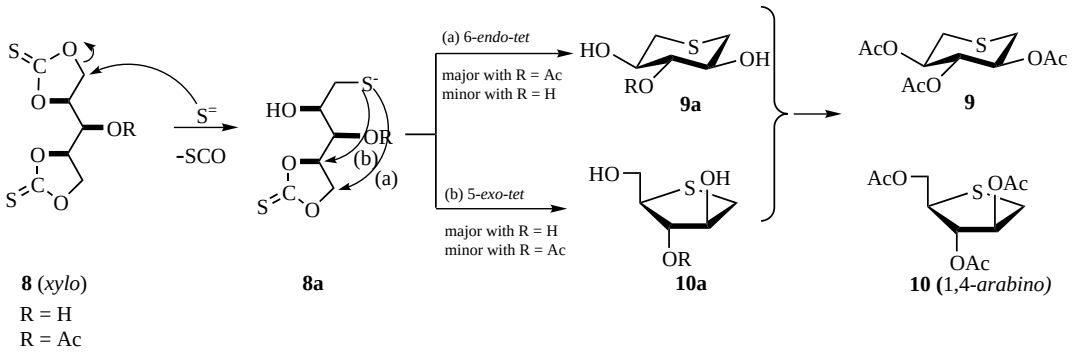
**Table 1.** Isolated yields of thiaheterocycles obtained via the vicinal bis-thionocarbonates of alditols. The latter were easily obtained from the alditol stannylene complex and phenyl thionochloroformate

| Entry | Substrats* | Bis-thionocarbonate Yield (%) | Thiaheterocycle[a] P = Ac, Yield (%) | Bis-thionocarbonate** P = Ac | Thiaheterocycle[a] Yield (%) |
|---|---|---|---|---|---|
| **1** |  Erythritol (**1**) |  **2** (97) | - | - |  **3** (50) |
| **2** |  D,L-Threitol (**4**) |  **5** (95) | - | - |  **6** (63) |
| **3** |  Xylitol (**7**) |  **8** (87) |  **9** (10 )  1,4-*arabino* **10** (40 ) |  **11** | **9**(68) **10** (8) |
| **4** |  Ribitol (**12**) |  **13** (63) |  **14** (32 )  (±) 2,5-*arabino* **15** (13 ) |  **16** | **14** (49) **15** (15) |
| **5** |  D-arabinitol (**17**) |  **18** (55) |  1,5-D-*arabino* **19**  1,4-D-*ribo* **20**  1,4-D-*xylo* **21** |  **22** | **19** (54) - - |
| **6** |  D-mannitol (**23**) |  **24** (69) | Complex mixture |  **25** |  **26** (68) |
| **7** |  Galactitol (**27**) |  **28** (90) |  (±) 2,6-*talo* (or 1,4-*alo*) **29** (37 ) |  **30** |  **31** (47)[b] |

*Stannylene acetal complexes of indicated alditols; **Obtained quantitatively from corresponding free bis-thionocarbonate; [a]Obtained after acetylation of crude product; [b]contaminated by a small amount of unknown by-product




**Scheme 1.**

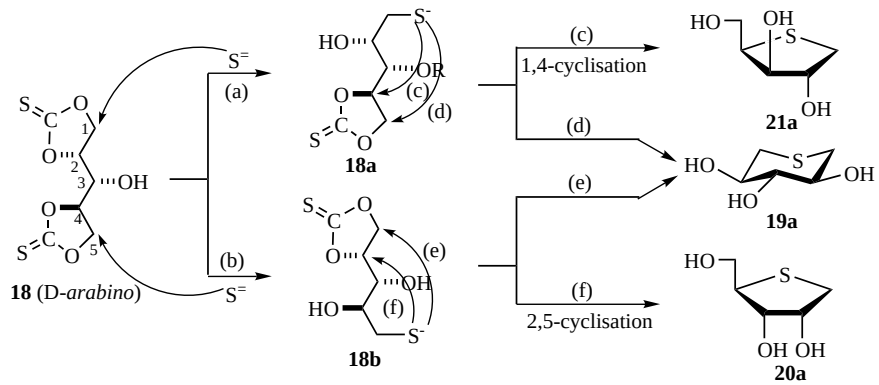
tion (**9** in 68% yield determined by $^{13}C$ NMR). This alternative regioselectivity in heterocyclisation can be attributed to steric hindrance created on the electrophilic site at C-4 (=C-2) by the acetate group.

In the case of the ribitol **12** (entry 4) the 6-*endo*-*tet* cyclisation appears to occur preferentially both with the bis-cyclic thionocarbonate derivatives **16** (acetylated at OH-3) and **13** (with free OH-3) (**14** formed in 49 and 32% yields, respectively). In both cases 5-*exo*-*tet* cyclisation was less preferred (**15** formed in 13 and 15% yields, respectively). While in the case of compound **16** as substrate, the steric hindrance of the acetate group at the C-3 position may be invoked to explain the product distribution, such an argument is not valid to explain that 5-*exo*-*tet* cyclisation in **13** is least preferred. In fact, in the case of **13**, it is the *cis*-vicinal arrangement of the two OH groups at C-3 and C-4 that hinders the formation of **15** obtained after acetylation.

With the D-arabinitol **17** (entry 5), the problem is more complex, given the dissymmetry of the bis-thionocarbonate derivatives **18** and **22** which could lead to the three thioanhydro products coming from 1,5, 1,4 and 2,5 cyclisations. The 3-*O*-acetylated bis-cyclic thionocarbonate **22** gave the tetrahydrothiopyrane derivative **19** as the sole product in 54% isolated yield. Protection of the OH-3 appears to play a determining role, since the bis-thionocarbonate **18** (free OH-3), gave a mixture of the three thioanhydro derivatives **19** (1,5-D-*arabino*), **21** (1,4-D-*xylo*) and **20** (1,4-D-*ribo*) with a total yield of 49% in the ratio of 5:4:1. The 5-*exo*-*tet* cyclisation obtained from a 2,5-thiaheterocyclisation (Scheme 2, path f) with inversion of the configuration of C-2 to give **20a** would be expected to be the least preferred in comparison with the 1,4-thiaheterocyclisation (path c) with inversion of the configuration of C-4 to give **21a**. As for compound **15**, this could be attributed to the *cis*-vicinal repulsion of the OH-4 and OH-3 in the transition state leading to ring **20a**.

A significant observation is the regioselective formation of the thiepane rings **26** (D-*manno*, 68%) and **31** (*galacto*, 47%) from the 3,4-di-*O*-acetyl-bis-cyclic thionocarbonte-D-mannitol (**25**) and the corresponding galactitol **30** derivatives (entries 6 and 7, respectively). In both cases the steric hindrance caused by the acetate groups on the electrophilic sites at C-2 and C-5 favoured the 7-*endo*-*tet* cyclisation. Paradoxically, when heterocyclisation of the bis-cyclic thionocarbonate **24** (D-*manno*) was attempted a complex mixture was obtained, while cyclisation of **28** (*galacto*) (both with free OH-3,4) exclusively gave the 2,6-thioanhydro-D,L-*talo* (or 1,4-D,L-*alo*) **29** in 37% yield with inversion of the configuration at C-5 (=C-2). Thus, the absence of protecting groups at C-3,4 in the bis-cyclic thionocarbonate of galactitol **28** (entry 7) favoured a 6-*exo*-*tet* cyclisation.

In this paper we report the first use of bis-cyclic thionocarbonates of linear polyols as bielectrophilic interme-




**Scheme 2.**

diates for the synthesis of polyhydroxylated tetrahydrothiophene, tetrahydrothiopyrane and thiepane derivatives. The originality of this transformation, and the ease with which the bis-cyclic thionocarbonate precursors are obtained make this an attractive alternative approach to the route from bis-epoxides, which are difficult to obtain for most alditols.

## Acknowledgements

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11. Procedure: The stannylenne acetal complexes obtained from alditols and $n$Bu$_2$SnO (2 equiv.) in toluene after azeotropic removal of water, were treated with PhOC(S)Cl (2.2 equiv.) in $HCCl_3$ as solvent for 4 h at rt with stirring. The corresponding bis-cyclic thionocarbonates were recovered by filtration (with galactitol)) or extracted by liquid chromatography in all others cases (eluant: $CH_2Cl_2$–acetone, 9:1 for tetritols and 8:2 for pentitols and D-mannitol)).