NOVEL REACTIONS OF CARBOHYDRATE DITHIANES: 1,4-DITHIEPINS VIA A 1,4-ALKOXY RELAY

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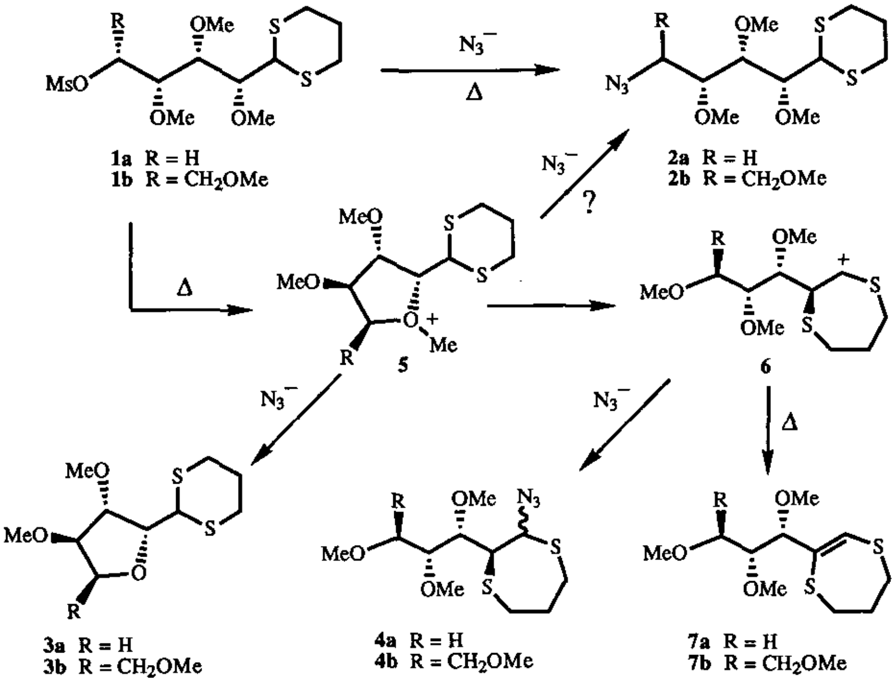
Abstract- When heated, 1,3-dithiane derivatives of common sugars which bear a mesylate at the 5-position (and are otherwise *O*-methylated) form 1,4-dithiepins by a novel mechanism in which ring expansion is coordinated with intramolecular relay of the 2-alkoxy group to the 5 position. Addition of a nucleophile such as azide to the reaction produces novel structures resulting from the trapping of intermediates along the pathway.

In the course of our efforts to do substitution reactions on various sugars, we have discovered an unexpected reaction of permethylated dithiane derivatives of xylose and glucose which bear a methanesulfonyloxy group at the 5 position (compounds **1a** and **1b**).[1] When the xylose derived *O*-methylated mesylate (**1a**) was added to 3.5 M LiN_3 in DMF at 100 °C, four products were formed in 77% overall yield. The expected primary azide (**2a**) constituted about 60% of the product mixture, but significant amounts of three unexpected products were also formed. The tetrahydrofuran derivative (**3a**) constituted about 25% of the product mixture, and the two diastereomeric 1-azides (**4a**) (in ~ 1 : 1 ratio) constituted about 15% of the product mixture. In the case of the glucose derived *O*-methylated mesylate (**1b**), addition to 3.5 M LiN_3 in DMF at 100 °C gave only a trace (<1%) of the direct displacement product (**2b**). The tetrahydrofuran derivative (**3b**) and the diastereomeric 1-azides (**4b**) were formed as essentially the sole products of the reaction in a 1 to 2 ratio in 82% yield.[2]

To explain the formation of the unusual products, we propose a mechanism in which the mesylate is expelled by the 2-methoxy group *via* a five membered ring transition state to form the oxonium intermediate (**5**).[3] This intermediate forms **3** by attack of azide at the methyl group. Alternatively, ring opening and sulfur migration gives carbonium ion (**6**), which is trapped by azide to yield **4**. It is uncertain whether product (**2**) is formed directly from **1**, or by attack of azide at the 5 position of the oxonium species (**5**).



To further probe the rearrangement, we pyrolyzed the mesylates in the absence of a nucleophile. When mesylate (**1a**) was heated to 100 °C in DMF, the 1,4-dithiepin (**7a**) was cleanly formed in 85% yield, presumably *via* intermediates (**5**) and (**6**).[4] When the glucose derived mesylate (**1b**) was treated similarly, the 1,4-dithiepin (**7b**) was formed as the sole product of the reaction in 88% yield. To the best of our knowledge, this is the first example of 1,4-dithiepin formation from a 1,3-dithiane having a remote leaving group.[5] It is also a novel example of an intramolecular 1,4-alkoxy transfer, which is a potentially useful phenomenon in carbohydrate chemistry.

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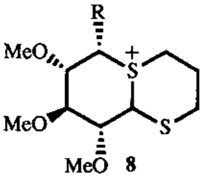
REFERENCES AND NOTES

1. Compounds (**1a**) and (**1b**) were prepared by permethylation of the appropriate methyl glycoside (MeI/NaH in DMF) followed by dithioacetal formation (1,3-propanedithiol/BF_3-OEt_2) and mesylation (MsCl/Et_3N).

2. The structure of **4b** was established *via* one bond (HMQC) and long range (HMBC) ^{1}H-^{13}C correlation 2-D nmr spectra. Although the two isomers were inseparable, their spectra could be assigned individually from the mixture. Selected data for isomer A: ^{1}H Nmr (500 MHz, $CDCl_3$) δ 5.21 (d, J = 1.9 Hz, H-1), 3.97 (dd, J = 1.8, 7.7 Hz, H-4), 3.60 (m, H5 and H6), 3.36 (s, 6-OCH_3), 3.30 (dd, J = 1.8, 10.3 Hz, H-2), 3.17 (dd, J = 1.8, 10.3 Hz, H-3), 3.09 and 2.94 (m, H-3'ab), 2.70 (m, H-1'b), 2.05 (m, H-2'ab). ^{13}C Nmr ($CDCl_3$) δ 81.28 (C-5), 79.97 (C-3 and C4), 72.55 (C-6), 65.04 (C-1), 60.69 (C-2), 33.15 (C-3'), 30.96 (C-2'), 24.06 (C-1'). Selected data for isomer B: ^{1}H Nmr (500 MHz, $CDCl_3$) δ 5.16 (d, J = 3.7 Hz, H-1), 4.06 (dd, J = 7.0, 2.6 Hz, H-4), 3.75 (dd, J = 8.8, 2.6 Hz, H-3), 3.67 (dd, J = 10.3, 2.9 Hz, H-6a), 3.60 (m, H-5), 3.38 (s, 6-OCH_3), 3.14 (dd, J = 8.8, 3.7 Hz, H-2), 3.01 (m, H-3'a), 2.70 (m, H-1'a), 2.60 (ddd, J = 3.7, 5.5, 15.4 Hz, H-3'b), 1.98 (m, H-2'ab). ^{13}C Nmr ($CDCl_3$) δ 81.22 (C-5), 79.71 (C-3), 79.56 (C-4), 72.34 (C-6), 67.09 (C-1), 52.06 (C-2), 31.13 (C-2'), 26.63 (C-3'), 25.16 (C-1'). Selected data for the mixture: FAB ms: 352 (M + H^+). Ir: 2100 cm^{-1}.

3. It is interesting to note that the sulfonium species (**8**) appears not to be formed productively, although sulfides are more nucleophilic than ethers, and the six membered transition state leading to **8** should be kinetically accessible. See for example Z. Sui, P. Furth, L. Fang, and J. De Voss, *J. Org. Chem.*, 1992, **57**, 6658 and J. Harness and N. Hughes, *J. Chem. Soc., Chem. Commun.*, **1971**, 811.



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4. The structure of **7a** was established via one bond (HMQC) and long range (HMBC) ^{1}H-^{13}C correlation 2-D nmr spectra: ^{1}H Nmr (500 MHz, C_6D_6) δ 6.00 (s, H-1), 3.69 (d, J = 6.7 Hz, H-3), 3.68 (m, H-4), 3.55 (dd, J = 10.3, 3.3 Hz, H-5a), 3.45 (s, 4-OMe), 3.44 (dd, J = 10.3, 5.4 Hz, H-5b), 3.21 (m, H-1'a and H-3'a), 3.13 (s, 5-OMe), 3.12 (s, 3-OMe), 2.95 (m, H-1'b & H-3'b), 1.59 (quintet, J = 6.1 Hz, H-2'). ^{13}C Nmr ($CDCl_3$) δ 133.6 (C-2), 120.0 (C-1), 88.0 (C-3), 82.3 (C-4), 73.2 (C-5), 59.7 (4-OMe), 59.1 (5-OMe), 56.5 (3-OMe), 32.0 (C-3'), 31.1 (C-2'), 30.9 (C-1'). FAB ms: 262 (M + H^+).

5. The formation of 1,4-dithiepins from dithioacetals having an α leaving group is known. See for example K. Saigo, Y. Hashimoto, L. Fang, and M. Hasegawa, *Heterocycles*, 1989, **29**, 2079.

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