Pergamon

Tetrahedron Letters, Vol. 37, No. 23, pp. 3925-3928, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00716-2

Intramolecular 1,3-Dipolar Cycloadditions of 5-Azido-5-deoxyaldopentose Ketene Dithioacetal Bis(sulfones) in the Synthesis of Imino Sugar Analogs

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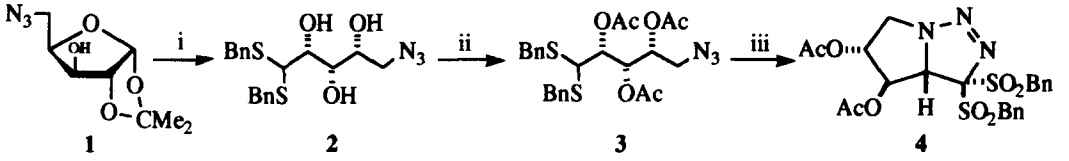
Abstract: Oxidation of the dithioacetal groups in the *O*-acetylated 5-azido-5-deoxy dibenzyl dithioacetal **3** of D-xylose and that (**7**) of D-ribose leads to triazoline derivatives **4** and **8**, the products of sequential oxidation to the bis(sulfones), loss of AcOH between C-1 and C-2 and, spontaneous intramolecular 1,3-dipolar cycloaddition of an azido ketene intermediate. A possible explanation of the observed diastereoselectivity is discussed. Copyright © 1996 Elsevier Science Ltd

The isolation, synthesis, and biological properties of imino sugars continues to be of interest since many of these compounds are capable of acting as inhibitors of glycoprocessing enzymes.[1] Reports have appeared in the literature detailing the synthesis of bicyclic triazoline[2] and tetrazole[3,4,5] imino sugar derivatives, several of which have been shown to be potent inhibitors of glycosidases. As part of our ongoing interest in the chemistry of sugar ω-azidodeoxy dithioacetals[6] we were interested in the synthesis of ω-azido ketene dithioacetal derivatives and their subsequent utility in the preparation of imino sugar analogs.

A previous attempt at using a sugar-derived ketene dithioacetal as a dipolarophile in intramolecular cycloadditions with an ω-azido substituent proved unsuccessful.[7] However, we know show here that exhaustive oxidation of the dithioacetal moiety of ω-azido D-xylose and D-ribose dibenzyl dithioacetals initiates a sequence of reactions resulting in the clean formation of bicyclic triazoline derivatives *via* intramolecular cycloaddition of the azide functionality to an *in situ*-generated ketene dithioacetal bis(sulfone). These compounds may be considered as bicyclic analogs of 1,4-dideoxy-1,4-iminopentitols such as the naturally occurring 1,4-dideoxy-1,4-imino-D-arabinitol.[8]

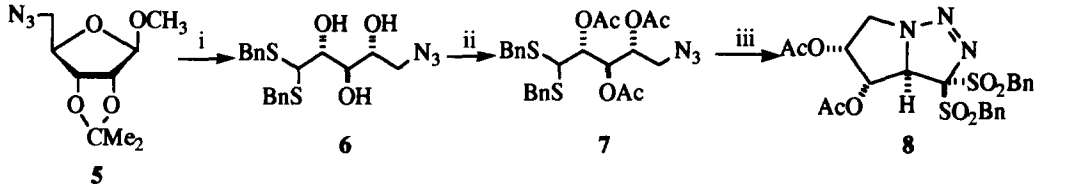
The known 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose[9] (**1**, Scheme 1) was converted into the dibenzyl dithioacetal derivative **2** (50%) by treatment with α-toluenethiol and trifluoroacetic acid. Conventional acetylation then afforded triacetate **3** (87%). Treatment of this derivative with an excess (4.2 equivalents) of *m*-chloroperoxybenzoic acid at 0° (in analogy with the MacDonald–Fischer reaction[10]) and subsequent stirring at room temperature for 8 h, afforded a single product formulated as the bicyclic triazoline **4** in 85% yield. Assignment of compound **4** as the diastereomer shown is based on a coupling constant of ~2 Hz between H-2 and H-3 of the pyrrolidine ring.[11] Examination of molecular models reveals that a much larger

coupling would be expected had the other possible diastereomer been formed by cycloaddition to the opposite face of the dienophile (*vide supra*).



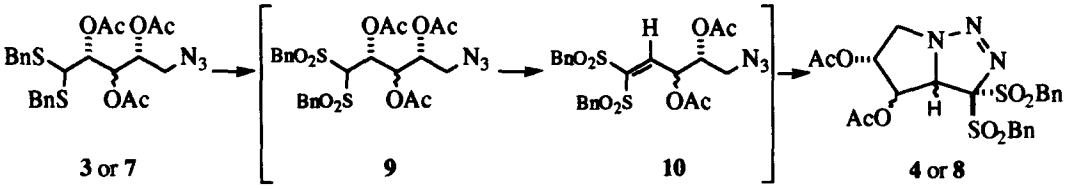
Scheme 1. *Reagents and conditions*: i. BnSH, CF_3CO_2H, $CHCl_3$, RT, 12 h. ii. Ac_2O, pyridine, RT, 12h. iii. *m*-CPBA (4.2 equiv), CH_2Cl_2, 0°–RT, 8 h.

The same sequence of transformations performed on methyl 1,2-*O*-isopropylidene-β-D-ribofuranose[12] (**5**) gave a similar result (Scheme 2). Treatment of **5** with α-toluenethiol and trifluoroacetic acid gave the dithioacetal **6** (55%) which was then protected as the triacetate **7** (90%). Exhaustive oxidation of **7** with excess *m*-CPBA again led to a single compound, identified as bicyclic triazoline **8** (92%). Again, the formulation of compound **8** as the diastereomer shown is based on the coupling constant between H-2 and H-3 of the pyrrolidine ring.[13] In this case, a $J_{2,3}$ value of 5.5 Hz could be reconciled only with the diastereomer shown.



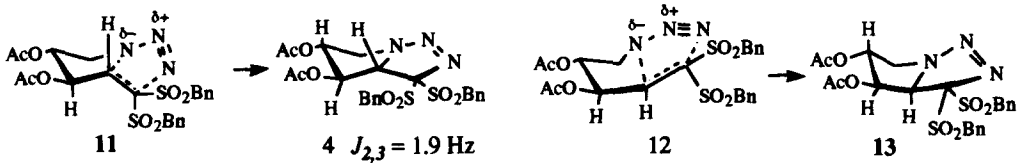
Scheme 2. *Reagents and conditions*: i. BnSH, CF_3CO_2H, $CHCl_3$, RT, 12 h. ii. Ac_2O, pyridine, RT, 12 h. iii. *m*-CPBA (4.2 equiv), CH_2Cl_2, 0°–RT, 8 h.

The formation of compounds **4** and **8** may be explained by a sequence involving exhaustive oxidation of the dithioacetal moieties in triacetates **3** or **7** to the corresponding bis(sulfones) (generally depicted as **9**, Scheme 3), loss of the elements of acetic acid between C-1 and C-2 to form ketene dithioacetal intermediates (**10**), and subsequent intramolecular dipolar cycloaddition to yield the triazoline products. It is noteworthy that the three steps in the formation of D-*xylo* compound **4** from **3**, and D-*ribo* analog **8** from **7**, occur in the same flask at low temperature, and result in the formation of only one diastereomeric product in each case.



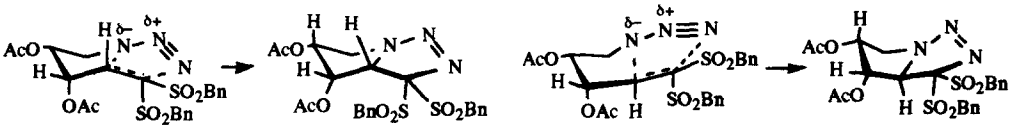
Scheme 3

The formation of only one of the two potential diastereomers during the 1,3-dipolar cycloaddition step, from both the D-*xylo* derivative **3** and the corresponding D-*ribo* analog **7**, can best be explained by considering the diastereomeric transition states possible in each case. For the D-*xylo* derivative **3**, dipolar cycloaddition of the azide can, in principle, occur at either of the two prochiral faces of the ketene dithioacetal bis(sulfone) function *via* two different transition states (T.S.). If the reaction proceeded through a T.S. such as **11** (Scheme 4), the "convex" product **4** would be formed and the coupling constant between H-2 and H-3 of the pyrrolidine ring would be expected to be small. The alternative situation, where the azide would add to the opposite face of the alkene, would proceed *via* a T.S. such as **12** and result in the "concave" bicyclic triazoline **13**. This compound would be expected to have a larger coupling between H-2 and H-3.



Scheme 4

Similarly, in the case of the D-*ribo* analog **7**, two diastereomeric T.S. are possible (**14** and **16**, Scheme 5) which would afford two diastereomeric products (**15** and **8** respectively). Proton NMR evidence in the D-*ribo* case indicates that **8** is formed exclusively ($J_{2,3}$ = 5.5 Hz) and thus T.S. **16** must be favored over the alternative **14**. A possible explanation for the different diastereoselectivity observed in the D-*xylo* and D-*ribo* series involves considering the configuration of the acetate group at C-3 of the sugar precursors (i.e. C-3 of the eventual pyrrolidine ring in **4** and **8**). In the D-*xylo* case (Scheme 4), the apparently favored T.S. **11** has the bulky $C(SO_2Bn)_2$ function aligned anti to the acetate group at C-3. The other potential situation (**12**) has the two groups aligned syn. A similar situation appears to occur in the D-*ribo* analog wherein T.S. **14** has the $C(SO_2Bn)_2$ and the C-3 acetate syn, whereas T.S. **16** has the two groups anti. It is possible that the preferential anti alignments of bulky adjacent functional groups in intermediates **10** (Scheme 3) account for the observed diastereoselectivity. The further utility of sugar ω-azido ketene dithioacetal derivatives in the synthesis of imino sugar derivatives is currently under investigation.



14 **15** **16** **8** $J_{2,3} = 5.5$ Hz

Scheme 5

Acknowledgements: We thank June Yun, Wesley White, Noel Whittaker, and Dr. Herman Yeh of the LAC, NIDDK, National Institutes of Health (Bethesda, MD) for help in obtaining NMR and mass spectra.

References and Notes

1. Fleet, G.W.J., Winchester, B., *Glycobiology* **1992**, *2*, 199-210.
   Legler, G., *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319-384.
2. Bernet, B., Buluso Murty, A.R.C., Vasella, A., *Helv. Chim. Acta* **1990**, *73*, 940-958.
   Buchanan, J.G., Edgar, A.R., Hewitt, B.D., *J. Chem. Soc. Perkin Trans. I* **1987**, 2371-2376.
3. Emert, P., Vasella, A., *Helv. Chim. Acta* **1991**, *74*, 2043-2053.
4. Davis, B., Brandstetter, T.W., Smith, C., Hackett, L., Winchester, B.G., Fleet, G.W.J., *Tetrahedron Lett.* **1995**, *36*, 7507-7510.
5. Brandstetter, T.W., Davis, B., Hyett, D., Smith, C., Hackett, L., Winchester, B.G., Fleet, G.W.J., *Tetrahedron Lett.* **1995**, *36*, 7511-7514.
6. Norris, P., Horton, D., Levine, B.R., *Tetrahedron Lett.* **1995**, *36*, 7811-7814.
7. Moss, W.O., Bradbury, R.H., Hales, N.J., Gallagher, T., *J. Chem. Soc. Perkin Trans. I* **1992**, 1901-1907.
8. Furukawa, J., Okuda, S., Saito, K., Hatanaka, S., *Phytochemistry* **1985**, *24*, 593-594.
   Nash, R.J., Bell, E.A., Williams, J.M., *Phytochemistry* **1985**, *24*, 1620-1622.
9. Jones, J.K.N., Szarek, W.A., *Can. J. Chem.* **1965**, *43*, 2345-2356.
10. MacDonald, D.L., Fischer, H.O.L., *J. Am. Chem. Soc.* **1955**, *77*, 4348-4350.
11. Compound **4**: mp 143-145 °C; $[\alpha]_D$ -258° (*c* 2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 10 H, Ph-H), 6.02 (bs, 1 H, H-3), 5.05 (d, 1 H, H-4, $J_{4,5'} = 3.0$ Hz), 4.83-5.24 (m, 4 H, CH_2Ph), 4.56 (d, 1 H, H-5, $J_{5,5'} = 13.5$ Hz), 4.54 (d, 1 H, H-2, $J_{2,3} = 1.9$ Hz), 3.85 (dd, 1 H, H-5', $J_{4,5'} = 3.0$ Hz, $J_{5,5'} = 13.5$ Hz), 2.18 (s, 3 H, OAc), 1.98 (s, 3 H, OAc); MS (CI, NH_3) 397 (M + 1 + NH_4^+ - SO_2CH_2Ph).
12. Brimacombe, J.S., Minshall, J., Tucker, L.C.N., *Carbohydr. Res.* **1976**, *52*, 31-47.
13. Compound **8**: syrup; $[\alpha]_D$ +137° (*c* 3.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 10 H, Ar-H), 5.81 (t, 1 H, H-3, $J_{2,3} = 5.5$ Hz, $J_{3,4} = 5.5$ Hz), 5.30 (dd, 1 H, H-4, $J_{3,4} = 5.5$ Hz, $J_{4,5'} = 5.5$ Hz), 4.76-5.01 (m, 4 H, CH_2Ph), 4.74 (d, 1 H, H-2, $J_{2,3} = 5.5$ Hz), 4.50 (dd, 1 H, H-5, $J_{4,5} = 5.5$ Hz, $J_{5,5'} = 12.5$ Hz), 3.76 (dd, 1 H, H-5', $J_{4,5'} = 5.5$ Hz, $J_{5,5'} = 12.5$ Hz); MS (CI, NH_3) 397 (M + 1 + NH_4^+ - SO_2CH_2Ph).

(*Received in USA* 9 *February* 1996; *accepted* 9 *April* 1996)