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Enantiospecific Synthesis of Heterocyclic Compounds: an Approach to Functionalised Tetrahydrofurans from Intramolecular Dipolar Cycloadditions

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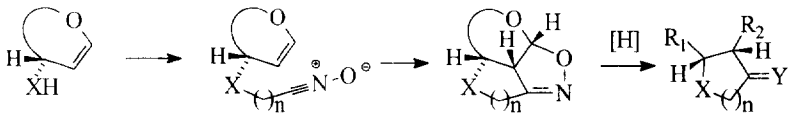
Abstract: *Intramolecular cycloaddition of the nitrone **8**, derived from the glucal **1**, produces stereospecifically the isoxazolidine **9** which may be reductively cleaved to afford functionalised aminotetrahydrofuran polyols such as **20** and **23***

The 1,3-dipolar cycloaddition of nitrile oxides and nitrones to alkenes has proved extremely useful in synthesis largely because the reaction usually proceeds in a highly stereocontrolled manner.[1] As a result of this appropriate reductive cleavage of the product isoxazolines and isoxazolidines has become an important approach towards a range of compounds such as β-hydroxyketones and β-aminoalcohols in diastereomerically pure form.[2] This has been further developed into enantiocontrol by using either a dipole [3] or a dipolarophile [4] containing a suitable chiral fragment, and more recently some success has been achieved in the use of chiral catalysts to promote enantioselection in reactions between achiral nitrones and alkenes.[5]

It is known that the reactions between vinyl ethers and nitrile oxides are regiospecific,[6] and we wish to report here the preliminary results from a study on the intramolecular cycloadditions to a chiral vinyl ether, a study which has the aim of developing a flexible general synthesis of a range of enantiomerically pure cyclic compounds. The essence of the overall approach is shown in scheme 1 for a nitrile oxide, although, as will be shown below, the idea is equally applicable with a nitrone as the dipole.

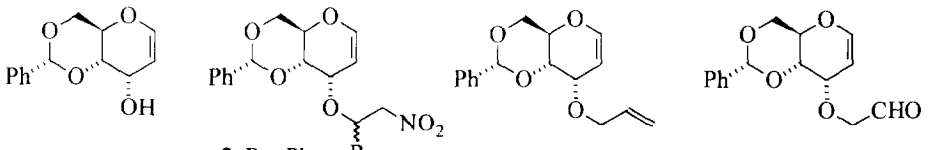
scheme 1



X = O, NH etc.; Y = O or NH_2/H

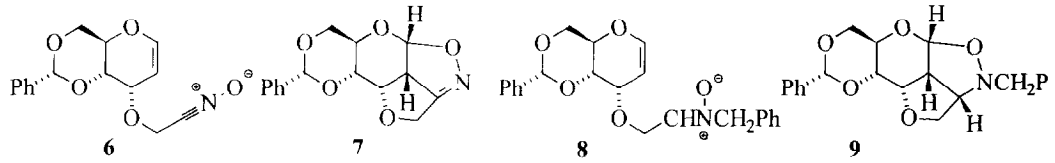
R_1, R_2 = functionalised side chains

Our studies began with the glucal **1** as this is readily available in a few steps from methyl-α-D-glucopyranoside.[7] Since nitrile oxides are readily available by dehydration of primary nitro compounds,[8] we tried to prepare the nitro compounds **2** and **3**. However, attempted conjugate additions to β-nitrostyrene gave no reaction under a range of conditions [9] and alkylations with α,ω-dibromoalkanes were unrewarding, again under a range of conditions, probably because the oxyanion from **1** preferred to act as a base; indeed, the only new product isolated from the reaction of the anion from **1** with 1,3-dibromopropane was the O-allyl ether **4**.



1 2, R = Ph 3, R = H 4 5

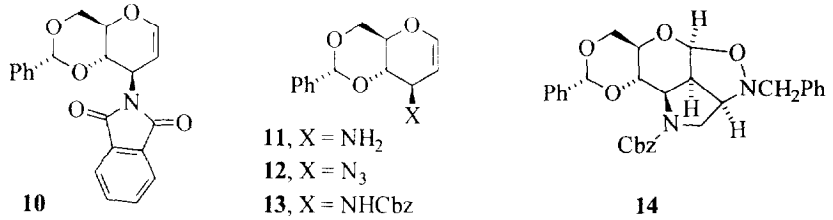
We therefore decided to approach a nitrile oxide via the aldehyde **5**, which was obtained by alkylation of **1** with methyl bromoacetate (KH, THF, 68%) followed by DIBAL reduction (ether, -78C), affording **5** (97%) as predominantly the hydrate.[10] Reaction of this aldehyde/hydrate mixture with hydroxylamine, followed by conversion to the nitrile oxide **6** (NCS, pyridine, DCM) allowed spontaneous intramolecular cycloaddition to provide the isoxazoline **7** , mp 149°C, (70% from **5**) as a single stereoisomer. Condensation of the aldehyde **5** with N-benzylhydroxylamine (ether, $CaCl_2$) [11] afforded the nitrone **8** which underwent cycloaddition on standing to give the isoxazolidine **9**, mp 147°C, (75%), again as a single stereoisomer.



6 7 8 9

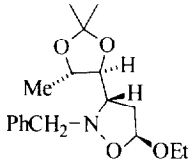
Compounds **7** and **9** contain a new heterocyclic ring, namely the tetrahydrofuran, and the cleavage of the molecules to release this unit will be discussed below.

Having succeeded in developing the route towards THF derivatives, we turned our attention towards pyrrolidines, which we planned to approach from **1** by replacing the OH group with a nitrogen based funtionality. Use of benzoate as the nucleophile in a Mitsunobu reaction with **1** has been reported to occur with allylic rearrangement leading to the 1-O-benzoate.[12] In contrast, we found that simple nucleophilic substitution occurred when **1** was treated with phthalimide under normal Mitsunobu conditions (Ph_3P, DEAD, THF) [13] affording the N-substituted phthalimide **10** (20%), but hydrazinolysis of **10** gave a complex mixture. A much more acceptable route towards the amine **11** involved treatment of **1** with diphenylphosphoryl azide/DBU in toluene at 25°C,[14] which gave the crystalline azide **12**, whose reduction (Ph_3P/DCM then aq. ammonia/THF)[15] delivered **11**. This was difficult to separate from the Ph_3PO by-product so the mixture was treated with CbzCl (DCM/aq. $NaHCO_3$) to provide the N-Cbz derivative **13**, mp 208-209°C, (65% from **1**) which was readily purified by recrystallisation. This was alkylated with methyl bromoacetate, reduced with DIBAL and converted to the N-benzylnitrone which cyclised in situ to provide the isoxazolidine **14**, mp 128-130°C (46% from **13**), using chemistry analogous to that developed in the oxygen series.

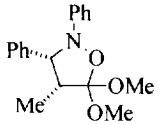


10 **11**, X = NH_2 **12**, X = N_3 **13**, X = NHCbz 14

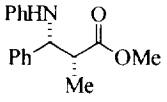
Reductive cleavage of the N-O bond in **7** and **9** and **14** has turned out to be unexpectedly difficult, although this does mirror the experience of De Shong [11] who found that the isoxazolidine **15** required rather more vigorous conditions than normal to effect cleavage, this presumably being caused by the oxygen of the original vinyl ether strenghthening the N-O bond in some way. More recently though there has been a report that the related isoxazolidine **16** is readily cleaved by hydrogenolysis to give **17**.[5(a)] The isoxazoline **7** showed little or no reaction with $LiAlH_4$,[16] H_2/Pd [17], Raney nickel [18] or a Zn/Cu couple.[19] The isoxazolidine **9** failed to react with $LiAlH_4$,[20] H_2/Pd [21] or Al/Hg,[22] but was cleaved with hydrogen and Pearlmann's catalyst in methanol / HCl [11] with the flask being placed in an ultrasonic bath to mimic the conditions of high pressure. The product **18** (51%) was highly reactive towards atmospheric carbon dioxide, an observation which has been previously reported with polyhydroxy amines.[23] A rather more amenable cleavage process began with conversion of **9** to the hygroscopic salt **19** (77%), by refluxing with benzyl bromide in ether (during this alkylation the benzylidene protecting group was always lost), followed by reduction of **19** with $LiAlH_4$ [24] (THF, reflux, 2 days) to provide **20** (68%), initially characterised as the tetraacetate **21**. Alternatively, treatment of the crude tetraol **20** with $NaIO_4$, followed by $NaBH_4$ reduction gave a mixture of the isomeric tetrahydrofuran diols **22** and **23**. We assumed that **23** was being produced by epimerisation of the intermediate aldehyde **24** under the basic conditions ($NaBH_4$/methanol) prior to reduction, and this was confirmed since overnight treatment of the crude $NaIO_4$ reaction product with a catalytic amount of sodium methoxide in methanol before addition of the $NaBH_4$ gave only the 2,3-trans isomer **23** (96%).[25]



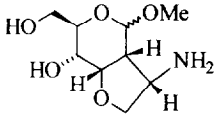
15



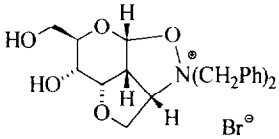
16



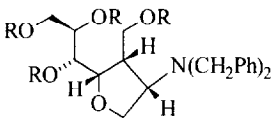
17



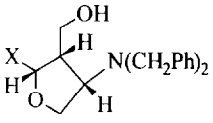
18



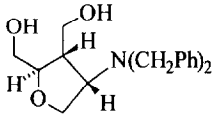
19



20, R = H
21, R = Ac



22, X = CH_2OH
24, X = CHO



23

The isoxazolidine **14** has also been converted to the N,N-dibenzyl salt corresponding to **19**, but reduction of this salt with $LiAlH_4$ has given only complex mixtures and we are now seeking other ways of cleaving isoxazolidines related to **14**.

Overall, we have demonstrated the viability of the approach depicted in scheme 1 and will report in due course our efforts to improve the crucial cleavage reactions and to modify the chemistry to allow access to other ring sizes.

Acknowledgements.

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References and Notes

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25. Selected spectral/physical data. **9**: m.p. 147°C; ν_{max} (KBr)/cm^{-1} 3380, 3320, 1720; δ_H(250 MHz; $CDCl_3$; *J*/Hz) 3.40 (1H, dd, *J*14.6, 7.3), 3.61-3.72 (3H, m), 3.80 (1H, dd, *J*9.5, 3.3), 3.95 (1H, d, *J*13.2), 4.11 (1H, d, *J*13.2), 4.20 (1H, dd, *J*7.5, 3.3), 4.44 (1H, dd, *J*10.4, 5.6), 4.57 (1H, dt, *J*9.8, 5.5), 5.50 (1H, d, *J*6.85), 5.60 (1H, s), 7.30-7.43 (8H, m), 7.55 (2H, m); δ_C(62.9 MHz; $CDCl_3$) 50.2, 59.8, 62.4, 69.8, 72.7, 72.8, 74.1, 78.0, 97.5, 102.7, 126.7, 128.0, 128.6, 128.9, 129.3, 129.4, 136.7 and 137.7; m/z (EI) 381.154, $C_{22}H_{23}NO_5$ requires 381.1576, . **23**: oil; δ_H(250 MHz; $CDCl_3$; *J*/Hz) 2.73 (2H, br s, OH), 3.50 (2H, d, *J*14.5), 3.6-3.85 (7H, m with d, *J*14.5 at 3.74), 3.93 (1H, m), 4.22 (1H,m); δ_C(62.9 MHz; $CDCl_3$) 42.5, 45.2, 55.2, 57.1, 61.8, 65.4, 81.3, 127.5, 127.7, 128.8, 129.1, 129.6, 138.4; m/z (EI) 327.186, $C_{20}H_{25}NO_3$ requires 327.1834.

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