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'Off-template site' intramolecular nitrone cycloaddition (INC) reactions on sugar-derived allylic ethers—a study on the substituent effect and synthesis of furano-pyrans†

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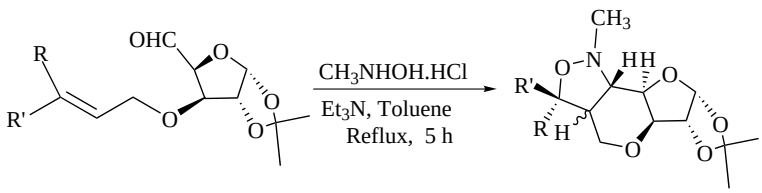
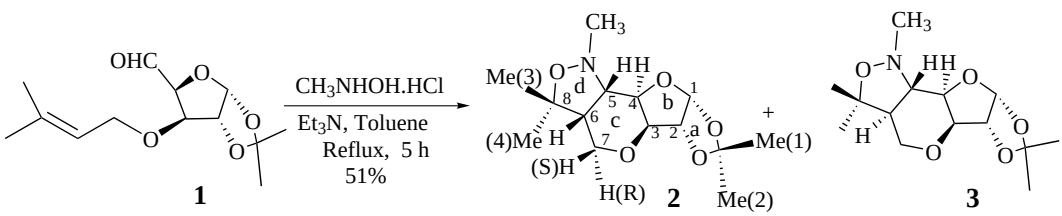
Abstract—Sugar-derived allylic ethers having one or two substituents on the terminal olefinic carbon centre were subjected to intramolecular nitrone cycloaddition (INC) reactions resulting in bicyclo[4.3.0] systems. The exclusiveness of product formation may be attributed to the effect of substituents. © 2001 Published by Elsevier Science Ltd.

Cycloaddition reactions, in particular 1,3-dipolar cycloaddition[1] reactions, play a prominent role in organic synthesis since the newly generated ring systems are highly amenable for further transformations leading to versatile intermediates. Fused *O*-heterocycles, such as furano- and pyrano-pyrans, being constituents of bioactive compounds,[2] are targets for synthetic organic chemists. Sugar based 1,3-dipolar cycloaddition products, either of intra- or intermolecular reactions, are highly useful chiral systems both for further elaboration and biological evaluation. Our recent work on the D-glucose-derived 3-*O*-prenyl ether, through the intramolecular oxime–olefin cycloaddition (IOOC) protocol, resulted in a new sugar-derived furano-pyran isoxazolidine,[3] the first sugar based isoxazolidine auxiliary. On the other hand, using the intramolecular nitrone cycloaddition (INC) protocol on D-glucose-derived 3-*O*-allyl ethers, Collins[4] and Bhattacharya[5,6] reported the synthesis of oxepane systems.[7] In continuation of our efforts[8–13] on the synthesis of new 'glycosubstances' from monosaccharides, herein we describe the results of the INC protocol on D-glucose-derived 3-*O*-allylic ethers and the effect of allylic substituents on the product formation (Eq. (1)).



(1)



Scheme 1.

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Accordingly, **1** (Scheme 1) derived[3] from D-glucose was subjected to an INC reaction with MeNHOH·HCl and Et_3N in toluene to afford a separable (silica gel, 60–120 mesh; ethyl acetate:petroleum ether, 1:9) mixture of **2** and **3** (2:1). The ^1H and ^{13}C NMR study indicated that **2** and **3** are fused rather than bridgehead isoxazolidines, since chemical shift of protons corresponding to a bridgehead methine were absent. Unlike our earlier results on IOOC reactions of **1** the two products obtained here should be epimeric at C (6). In the ^1H NMR spectrum of **2**, the coupling constant of 11.7 Hz for $J_{H6–H7\ (pro\text{-}R)}$ indicates a 1,2-diaxial disposition in a chair conformation, while $J_{H4–H5}=1.8$ Hz suggests that H5 is *trans* to H4 with the (*S*)-configuration at C5. Small values of the couplings involving the protons at the centres of ring fusion are consistent with the *cis* stereochemistry for all the three five-membered rings a, b and d. The inter ring NOE shown in Fig. 1 confirmed the envelope conformation for rings a and d. The flagpole–flagpole and 1,3-diaxial proximities between H3–H6, H4–H6 and H5–H7 (pro-*S*) in the NOE studies on **3** (Fig. 1) amply indicate a distorted boat structure for the pyran ring and infer a *trans*-fused isoxazolidine ring unlike that in **2**. The coupling constants $J_{H5–H6}=12.8$ Hz, $J_{H6–H7\ (pro\text{-}R)}=8.3$ Hz and $J_{H6–H7\ (pro\text{-}S)}=11.2$ Hz agree well with the proposed configuration.

Thus, from extensive NMR studies it was evident that (a) unlike the case of the 3-*O*-allyl ether, the INC reaction of 3-*O*-prenyl ether gave furano-pyrans exclusively and (b) unlike the case of the IOOC reaction of 3-*O*-prenyl ethers, the corresponding INC reaction resulted in *cis*- and *trans*-fused isoxazolidines. These results could well be attributed to the steric effect of the methyl groups that are present on the allylic double bond.

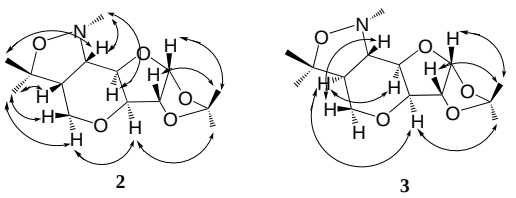
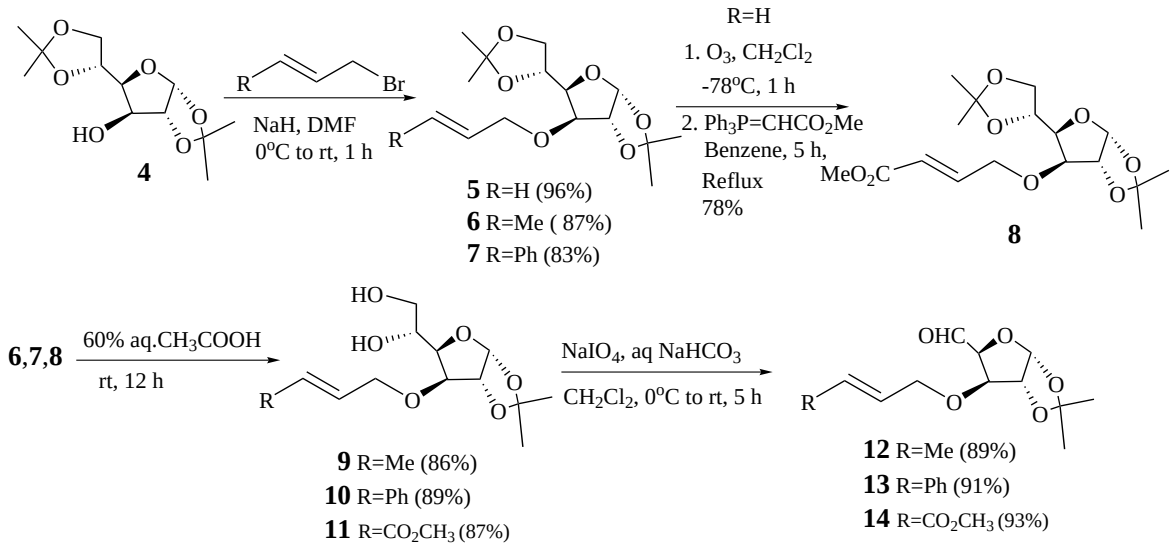


Figure 1.

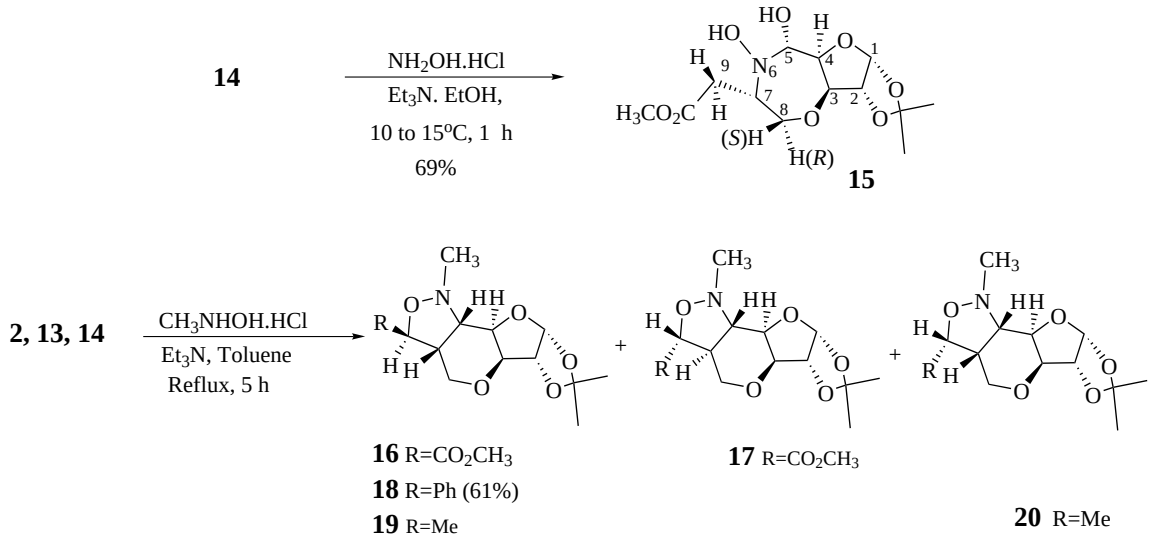
Having observed disparities in the IOOC and INC reactions on **1** giving *cis*- and *cis*/*trans*-fused products, the study was extended to the mono substituted allylic ethers **12–14**, prepared from diacetone glucose **4**. Accordingly, **4** on reaction (Scheme 2) with crotyl and cinnamyl chlorides gave the corresponding ethers **6** and **7**, respectively, while the known[14] allyl ether **5**, was subjected to ozonolysis and Wittig olefination ($Ph_3P{=}CH–CO_2Me$, benzene, Δ) to give **8**. Hydrolysis of **6–8** (60% aq. AcOH) and oxidative cleavage of diols **9–11** with $NaIO_4$ gave **12–14**, respectively.

Compound **14** on an IOOC reaction (Scheme 3) with $NH_2OH·HCl$ and Et_3N in ethanol gave **15**. From extensive ^1H and ^{13}C spectral analysis it was evident that **15** is neither a fused nor a bridged isoxazolidine, but an oxazepine derivative. The observation of an NOE between H3–H8 (pro-*R*) as well as between H5–H7 implies their diaxial disposition, while the vicinal coupling $J_{H7–H8\ (pro\text{-}R)}=11.4$ Hz and $J_{H7–H8\ (pro\text{-}S)}=4.2$ Hz suggests that H7 and H8 (pro-*R*) are *trans* to each other. This unambiguously indicates that H3 and H8 (pro-*R*) are on one side, while H5 and H7 are on the opposite side of the seven-membered ring, which takes a deformed chair structure. The other characteristic NOEs which further support the structure are shown in Fig. 2. Thus the formation of **15** is the result of a Michael addition and concomitant cyclisation reaction of NH_2OH.

Aldehyde **14**, when subjected to an INC reaction with MeNHOH·HCl–Et_3N in toluene at reflux, afforded a mixture of **16** and **17** (59%; 2:1), which were found to be fused isoxazolidines similar to **2** and **3**. The cou-



Scheme 2.



Scheme 3.

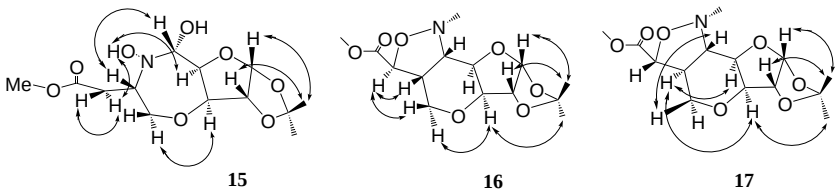


Figure 2.

plings and NOE results for **16** were very similar to those of **2** with the NOE of H8 with H7 (pro-*S*) and H7 (pro-*R*), indicating H8 to be *trans* to H6 with the (*S*)-configuration at C8 (Fig. 2). The results from **17** were similar to those of **3**. The presence of an H8–H5 NOE supports the (*R*)-configuration at C8, H8 being *trans* to H6 (Fig. 2). Further confirmation was obtained from the NOE between H8 and H7 (pro-*S*).

Similarly, the INC reaction on **13** (R = Ph) gave **18** as the exclusive product, which was identified from extensive spectroscopic data, while **12** (R = Me) afforded a mixture of **19** and **20** (66%) in a 9:1 ratio. The ring junction stereochemistry was unambiguously assigned from NMR data. Adduct **19** has a structure similar to that of **16**, whereas **20** is the epimer of **19** at C-8. Additional NOEs between Me-3 with H5 in **19** and Me-3 with H7 (pro-*R*), H7 (pro-*S*) in **20**, further supported the assigned stereochemistry.

The regiochemical outcome of the present study with the exclusive formation of bicyclo[4.3.0] systems may be attributed to the flexibility in the transition state (Fig. 3). In the preferred transition state (**A**), due to the presence of substituent(s) at the terminal olefinic carbon, the formation of the *exo* isomer is highly favoured due to steric reasons.

Thus, in conclusion we have reported substituent effects on the intramolecular 1,3-dipolar cycloaddition of 3-*O*-allylic ethers, where unlike in the case of an allyl ether, under INC conditions, the furano-pyrans are obtained as exclusive products, rather than the oxepanes, which may be attributable to the steric effect of the substituents. Similarly, the IOOC reaction on the allylic ether (with CO_2Me) gave an oxazepine ring while an isoxazolidine was obtained from the INC reaction. The substituent effect is clearly evident in the exclusive formation of fused isoxazolidines, where additional stereocentres can be incorporated for further manipulations. Additional work on the synthesis of fused isoxazolidines as chiral linkers is in progress in our laboratories.

Acknowledgements

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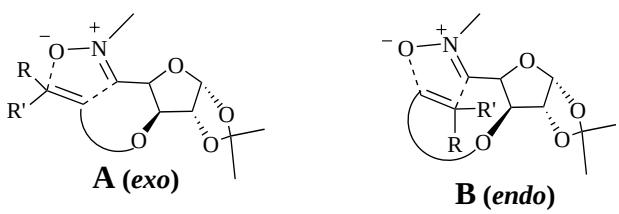

Figure 3.

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