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Intramolecular 1,3-dipolar nitrone and nitrile oxide cycloaddition of 2- and 4-*O*-allyl and propargyl glucose derivatives: a versatile approach to chiral cyclic ether fused isoxazolidines, isoxazolines and isoxazoles

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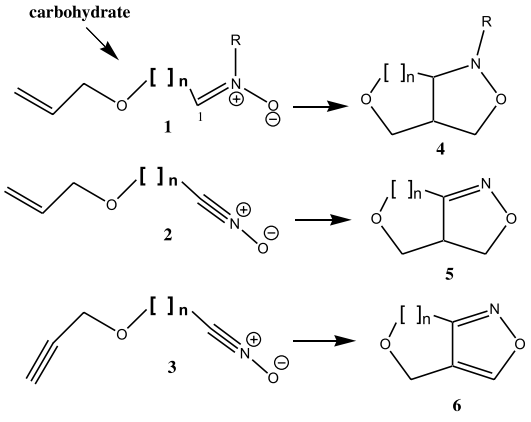
Abstract—2-*O*- and 4-*O*-Allyl and -propargyl glucose and the corresponding oxime derivatives were prepared from readily available glucose dithioacetals. Intramolecular 1,3-dipolar cycloaddition of the *N*-benzyl and *N*-methyl nitrones of the above acyclic 2-*O*-allyl glucose derivatives led to the diastereoselective formation of chiral isoxazolidines incorporating the tetrahydrofuran ring. The EI mass spectra revealed a characteristic cleavage of the C-alkyl group adjacent to the furan oxygen atom. An enantiopure trisubstituted tetrahydrofuran was obtained by the reductive cleavage of the isoxazolidine ring of one of the cycloadducts. In contrast, the nitrile oxide cycloaddition of the 2-*O*-allyl derivatives afforded diastereomeric mixtures of the corresponding dihydroisoxazolines, the stereochemistry of which was tentatively assigned on the basis of the principle of optical superposition. The exclusive formation of a tetrahydrofuran ring from pentaallyl nitrone or nitrile oxide demonstrated the preferred formation of a five-membered ring to that of six or seven-membered rings. The nitrile oxide generated from a 3,4,5,6,7-pentaallyloxy-1-nitroheptane derivative obtained from pentaallylglucose underwent diastereoselective cycloaddition to give an isoxazoline fused to a pyran ring. Enantiopure isoxazoles containing tetrahydrofuran and oxepane rings were also prepared in good yields by the nitrile oxide cycloaddition of the 2-*O*- and 4-*O*-propargyl derivatives.

1. Introduction

One of the frequently used strategies employed for the synthesis of heterocyclic compounds is the 1,3-dipolar cycloaddition reactions involving a nitrone or nitrile oxide and an alkene or alkyne.[1–4] Recently, these two cycloaddition reactions have been successfully applied to *O*- and *N*-alkenylcarbohydrate derivatives leading to the synthesis of enantiomerically pure cyclic ethers and amines fused to isoxazolidine and dihydroisoxazoline rings.[5–7] Most of these cycloadditions have been applied to 3-*O*-allyl carbohydrate derivatives giving rise to pyran and oxepane rings.[8] Examples of the synthesis of tetrahydrofuran rings from carbohydrate derivatives by employing these cycloadditions have remained scarce.[9–11] Earlier, we reported the formation of tetrahydrofuran rings via the nitrone cycloaddition of acyclic 2-*O*-allyl glucose derivatives.[9] Herein, we describe in detail the earlier work[9] and hitherto unreported nitrile oxide cycloaddition of acyclic 2-*O*- and 4-*O*-allyl and propargyl glucose derivatives leading to enantiopure isoxazolidine, dihydroisoxazoline and isoxazole ring fused tetrahydrofuran, pyran and oxepane derivatives.

The general strategy for the above cycloaddition reactions is depicted in Scheme 1. A nitrone or nitrile oxide



Scheme 1. *O*-Allyl and -propargylcarbohydrate nitrone and nitrile oxide cycloaddition strategy.

Keywords: Nitrone; Nitrile oxide; Cycloaddition; Glucose; Isoxazolidine; Isoxazoline; Isoxazole.
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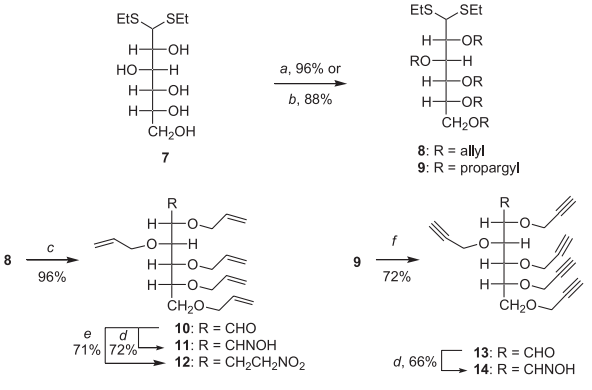
functionality is generated at the 1-C of an acyclic glucose derivative having a 2-*O*- or 4-*O*-allyl or propargyl moiety corresponding to the values of $n=1$ and 3. The nitrone **1** or the nitrile oxides **2** and **3** formed in this manner undergo cycloaddition to afford an isoxazolidine **4**, a dihydroisoxazoline **5** and an isoxazole **6**, respectively. A noteworthy feature of this strategy is the availability of different sizes of cyclic ethers fused to diverse types of heterocyclic rings.

2. Results and discussion

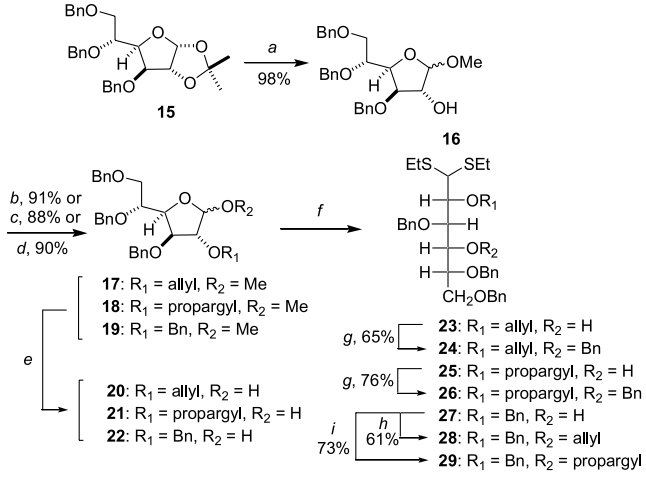
2.1. Preparation of the nitrone and nitrile oxide precursors

The nitrones used in this work were prepared from the reaction of the corresponding aldehydes and *N*-benzylhydroxylamine or *N*-methylhydroxylamine, whereas nitrile oxides were generated from the corresponding aldoximes using chloramine-T,[12] and in one case from a primary nitro compound using 4-chlorophenyl isocyanate.[13] The starting acyclic aldehydes were prepared by the cleavage of the corresponding dithioacetals, which were obtained from readily available glucose derivatives according to Scheme 2. The glucose dithioacetal **7**[14] was converted to the pentaallyl and pentapropargyl derivatives **8** and **9** by alkylation with allyl bromide and propargyl bromide using sodium hydride in DMF. The dithioacetal **8** was converted to the aldehyde **10** by treatment with $HgCl_2$ and $CaCO_3$ in aqueous acetonitrile.[15] The aldehyde **10** and other aldehyde intermediates in this study were used directly for the next steps, because they were found to be sensitive to chromatographic purification. The penta-*O*-propargyl glucose dithioacetal **9** was converted to the aldehyde **13** by a two-step procedure involving oxidation with $NaIO_4$ followed by treatment of the crude sulfoxide intermediate with H_2SO_4 and THF,[16,17] because the direct $HgCl_2$ mediated cleavage of **9** failed to afford **13**. The aldehydes **10** and **13** were converted to the respective oximes **11** and **14** by treatment with $NH_2OH.HCl$ in pyridine–methanol. The primary nitro derivative **12** was prepared from **10** by following a known protocol[18] involving treatment with nitromethane and acetylation followed by reduction with $NaBH_4$ without isolation of the intermediates (Scheme 2).

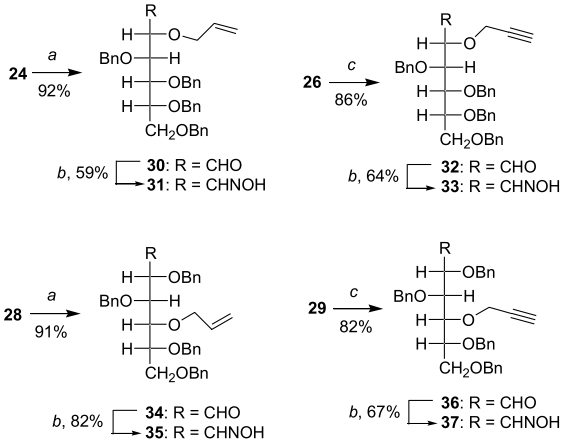


Scheme 2. Synthesis of penta-*O*-allyl and penta-*O*-propargyl glucose, their respective oximes and the nitro derivative **12**. Reagents and conditions: (a) NaH, allylbromide, DMF, 25 °C, 12 h; (b) NaH, propargylbromide, DMF, 25 °C, 12 h; (c) $HgCl_2$, $CaCO_3$, CH_3CN–H_2O (4:1), 25 °C, 6 h; (d) $NH_2OH.HCl$, pyridine, MeOH, reflux, 8 h; (e) (i) CH_3NO_2, KF, 2-propanol, 25 °C, 15 h, (ii) Ac_2O, DMAP, CH_2Cl_2, 25 °C, 12 h, (iii) $NaBH_4$, EtOH, 0–25 °C, 6 h; (f) (i) $NaIO_4$, EtOH, 25 °C, 10 h, (ii) THF, conc H_2SO_4, 25 °C, 12 h.

Another set of acyclic intermediates were prepared from the 1,2-isopropylidene glucose derivative **15**,[19] which was converted to the methyl glycoside **16** as an anomeric mixture, alkylation of which with allyl bromide, propargyl bromide and benzyl bromide separately afforded the anomeric mixtures of the 2-*O*-allyl, 2-*O*-propargyl and 2-*O*-benzyl derivatives **17**, **18** and **19**, respectively (Scheme 3). Although, the respective α and β anomers in the mixtures could be separated by column chromatography, in this study the mixtures were used without separation for the next steps viz. deglycosylation to **20**, **21** and **22** and dithioacetylation to **23**, **25** and **27** followed by alkylation of the 4-OH with either benzyl or allyl or propargyl bromide giving rise to the dithioacetal derivatives **24**, **26**, **28** and **29**.



Scheme 3. Synthesis of 2-*O*- and 4-*O*-allyl and -propargyl glucose dithioacetals. Reagents and conditions: (a) *p*-TsOH, MeOH, reflux, 6 h; (b) allylbromide, Bu_4NBr, CH_2Cl_2, 50% aq NaOH, 25 °C, 12 h; (c) propargylbromide, Bu_4NBr, CH_2Cl_2, 50% aq NaOH, 25 °C, 12 h; (d) benzylbromide, Bu_4NBr, CH_2Cl_2, 50% aq NaOH, 25 °C, 12 h; (e) 50% aq TFA, 25 °C, 24 h, **20** (96%), **21** (94%), **22** (89%); (f) EtSH, conc H_2SO_4, 0 °C, 20 h, **23** (81%), **25** (76%), **27** (73%); (g) NaH, benzylbromide, THF, 25 °C, 12 h; (h) NaH, allylbromide, THF, 25 °C, 12 h; (i) NaH, propargylbromide, THF, 25 °C, 12 h.



Scheme 4. Synthesis of 2-*O*- and 4-*O*-allyl and -propargyl glucose oximes from their dithioacetals. Reagents and conditions: (a) $HgCl_2$, $CaCO_3$, CH_3CN:H_2O (4:1), 25 °C, 6 h; (b) $NH_2OH.HCl$, pyridine, MeOH, reflux, 8 h; (c) (i) $NaIO_4$, EtOH, 25 °C, 10 h, (ii) THF, conc H_2SO_4, 25 °C, 12 h.