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Intramolecular Nitrile Oxide−Alkene Cycloaddition of Sugar Derivatives with Unmasked Hydroxyl Group(s)

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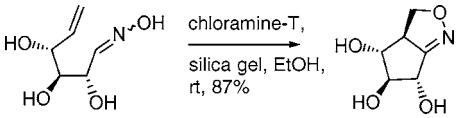
ABSTRACT

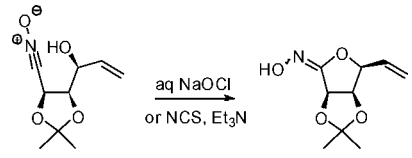


oxime isoxazoline

Intramolecular nitrile oxide−alkene cycloaddition (INOC) of sugar derivatives with one to four free hydroxyl group(s) is reported. The INOC reaction, using chloramine-T, in the presence of silica gel, to generate nitrile oxides from oximes, proceeded smoothly to afford five- or six-membered carbocycles in good to excellent yields. This new methodology alleviates protection/deprotection steps and makes the synthetic route shorter and more efficient.

Intramolecular nitrile oxide−alkene cycloaddition (INOC) and intramolecular nitrone−alkene cycloaddition (INAC) are versatile synthetic tools for the fabrication of fully functionalized carbocycles of different ring sizes from sugars.[1a−c] The heavily oxygenated carbocycles prepared via the INOC reaction are valuable precursors for the syntheses of cyclopentanoid and cyclohexanoid natural products and analogues. Examples are cyclophellitol,[1d] trehazolin,[1e] (+)-gabosines C and E,[1f] glycosidase inhibitors aminocyclopentitols,[1g] and carbocyclic nucleosides noraristeromycin and neplanocin A.[1h]

Scheme 1. Formation of Oximolactone **2** (an Undesired Reaction)



nitrile oxide **1** oximolactone **2**

Magnesium ion mediated intermolecular cycloaddition of nitrile oxides with allyl alcohols is known,[1i−k] but the alcohol in nitrile oxide is protected.[1i] Most INOC reactions of sugar derivatives proceed with masked hydroxyl groups.[1d,g,h,2] Only two examples have been realized in the presence of a free hydroxyl group at the δ position.[3] INOC of sugar derivatives with free hydroxyl group(s) present in other positions

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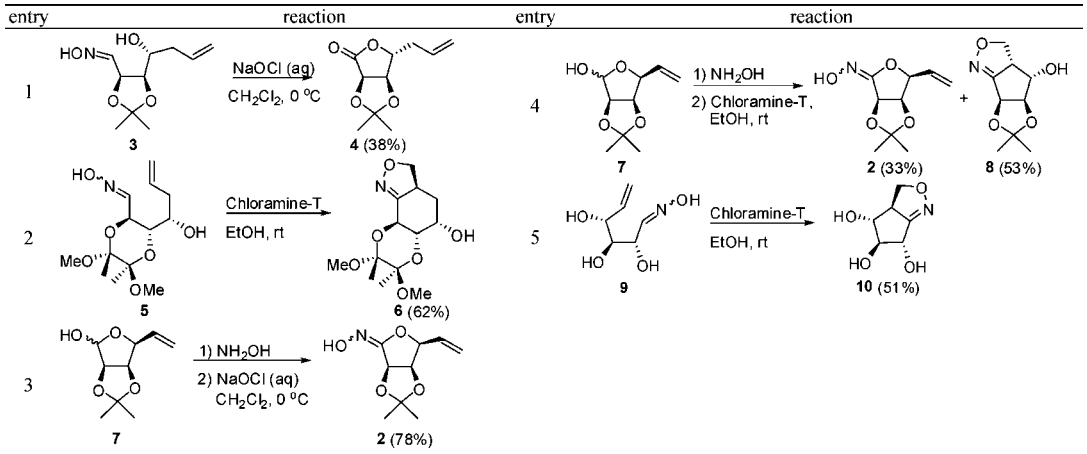
Table 1. INOC of Substrates **3**, **5**, **7**, and **9** under Different Conditions

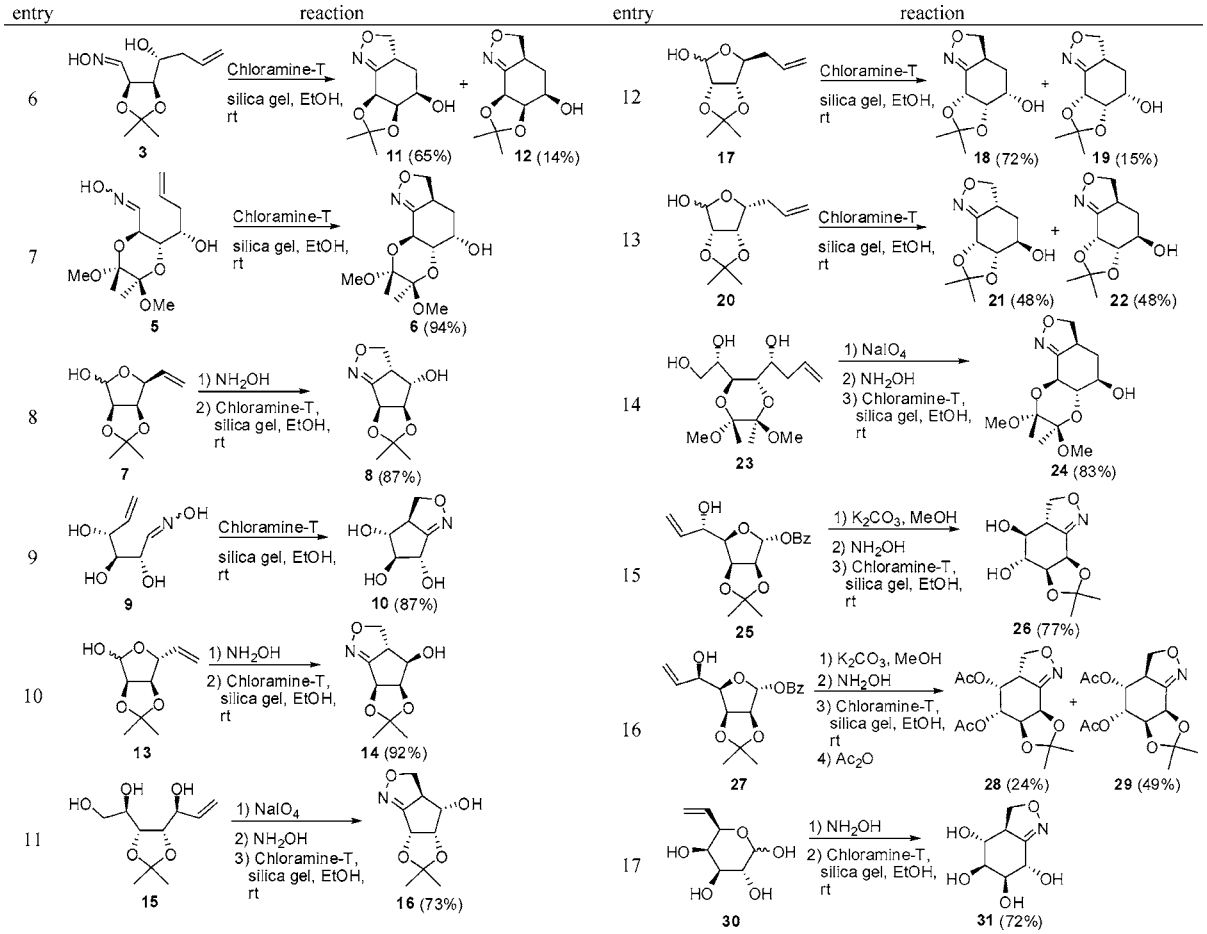


has not been reported. This paper describes, using chloramine-T/silica gel to generate nitrile oxide from oxime, successful INOC of sugar derivatives with free hydroxyl groups that alleviate protection/deprotection steps which, in turn, renders the various synthetic schemes shorter and more efficient.

The nitrile oxides derived from sugars are highly oxygenated, and the free hydroxyl group, when present, could attack the electrophilic carbon of nitrile oxide **1**, forming oximolactone **2**[4] as the side product (Scheme 1 and entry 3 in Table 1).

Common reagents for the conversion of oxime into nitrile oxide include NaOCl, NaOCl with NEt_3, and *N*-chlorosuccinimide with NEt_3.[5] Such reaction conditions are basic enough to deprotonate the hydroxyl function and increase

Table 2. INOC Using Chloramine-T and Silica Gel



its nucleophilicity. Hence, the formation of the undesired oximolactone product is enhanced. A new nonbasic method for the transformation of oximes derived from sugars into nitrile oxides is therefore warranted. Reaction of oxime **3** with aqueous NaOCl gave an oximolactone that was hydrolyzed immediately to afford lactone **4**[6] in 38% yield (entry 1). Stirring oximes **5** or **9** with aqueous NaOCl resulted in decomposition of the starting material and provided no cycloadducts. Condensation of lactol **7** with NH_2OH afforded an oxime that was oxidized with aqueous NaOCl to give the unwanted oximolactone **2**[4] exclusively (entry 3).

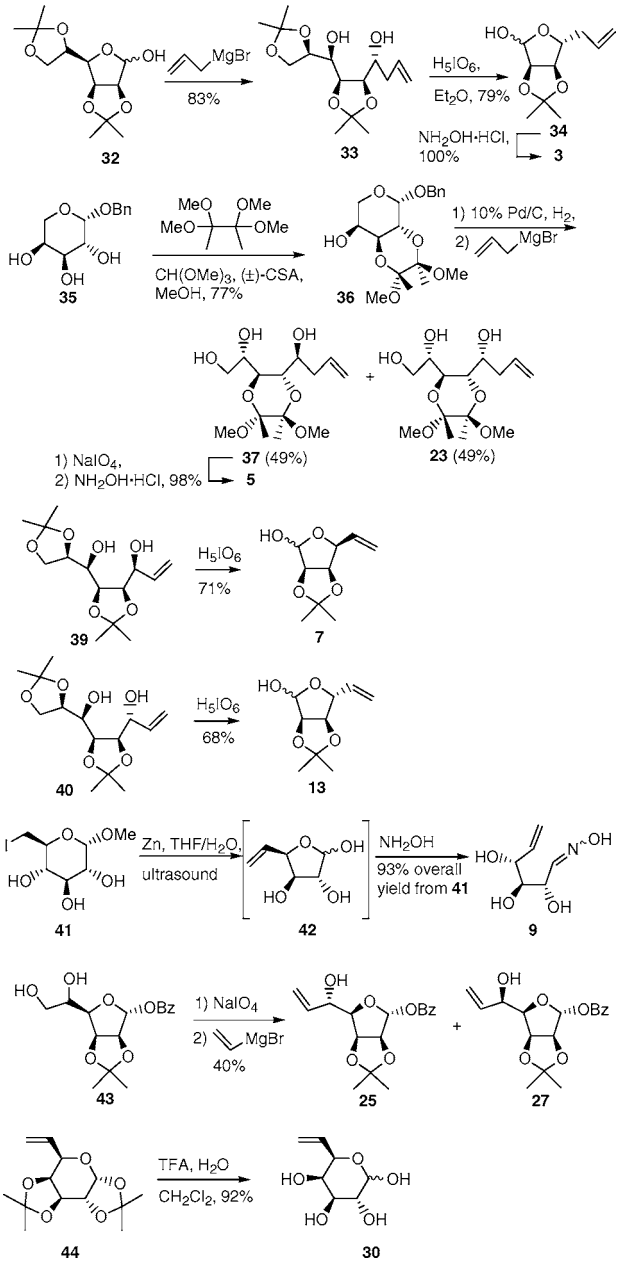
Chloramine-T[7] has been reported for the generation of nitrile oxides from oximes, and by applying such conditions to oxime **5**, the oxime derived from lactol **7**, and oxime **9**, the corresponding isoxazolines **6**, **8**,[8] and **10**[9] were obtained, respectively, but in moderate yields (entries 2, 4, and 5). The formation of the undesired oximolactone **2** might be the major reason for the moderate yields (entry 4).

Silica gel was therefore added together with chloramine-T to attain a slightly acidic environment for the INOC reactions of substrates having one to four free hydroxyl group(s), and the results are summarized in Table 2. With this new methodology, isoxazolines **11** and **12** were obtained for the first time from oxime **3** in a combined yield of 79% (entry 6). Oxime **5** now gave a much improved 94% yield of isoxazoline **6** (entry 7, cf. entry 2). Similar improvements in reaction yields were also observed with substrates **7** and **9** (entries 8 and 9). Applying the silica gel mediated reaction conditions to other substrates afforded the desired five-membered or six-membered carbocycles in good to excellent yields (entries 10−17). For substrate **27**, two isoxazolines were obtained after the INOC reaction which were inseparable by column chromatography; these were converted into the acetates **28** and **29** to allow chromatographic separation. The combined overall yield for the four-step transformation was a respectable 73%.

All the substrates employed for the INOC reactions were synthesized from carbohydrates, and their preparations are shown in Scheme 2.

Diacetonide **32**,[10] readily available from D-mannose, reacted with excess allylmagnesium bromide to give alkene

Scheme 2. Preparation of Substrates



33 with 5:1 diastereoselectivity. Selective hydrolysis of the terminal isopropylidene group in **33**, followed by glycol oxidative cleavage, was performed with periodic acid[11] in one pot to furnish lactol **34** in 79% yield. Oximation of lactol **34** then gave substrate **3** in quantitative yield. Benzyl-β-L-arabinopyranoside **35**,[12] prepared from glycosidation of L-arabinose, was protected with a *trans*-diacetal ring to give acetal **36**. Upon hydrogenolysis and allylation, alkenes **37** and **23** were harvested from **36** in equal amounts. Alkene **37** was then converted into substrate **5** by glycol oxidative cleavage and oximation. Alkenes **39** and **40**, prepared from

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(8) The X-ray structure of the enantiomer of the acetate derivative of **8** was published by Professor V. Jäger. See: Gültekin, Z.; Frey, W.; Jäger, V. *Z. Kristallogr. - New Cryst. Struct.* **2002**, *217*, 405−406.

(9) Structure confirmed by comparing the spectroscopic data of the acetate derivative. See: (a) Henkel, S.; Kleban, M.; Jäger, V. *Z. Kristallogr. - New Cryst. Struct.* **1997**, *212*, 53−54. (b) Hilgers, P. Dissertation, Universität Stuttgart, 1996. (c) Kleban, M. Dissertation, Universität Stuttgart, 1996.

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D-mannose according to the literature,[13] were readily transformed into substrates **7** and **13** with periodic acid.

Iodide **41**, constructed from methyl-α-D-glucopyranoside,[14] was reacted with zinc[15] to give lactol **42** that was converted into substrate **9** after oximation. Substrates **15**,[13] **17**,[16] and **20**[16] were prepared from D-ribose according to the literature. Diol **43** was obtained from D-mannose in three steps.[17] Glycol oxidative cleavage of diol **43**, followed by vinylation, afforded substrates **25** and **27** in equal amounts. Starting from D-galactose, alkene **44** was prepared in three steps.[18] Acid hydrolysis of alkene **44** with TFA furnished substrate **30** in 92% yield.

To conclude, INOC reactions that use chloramine-T and silica gel in ethanol to generate the nitrile oxide from the oxime proceed smoothly with unmasked hydroxyl group(s) to give the desired isoxazolines in good to excellent yields. A general method for the construction of highly functionalized five- and six-membered carbocycles from sugar derivatives via the INOC strategy is now revealed. This new methodology alleviates protection/deprotection steps and makes the entire synthetic avenue shorter and more efficient.

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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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