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Synthesis and radical fragmentation of carbohydrate anomeric nitrates. Formation of convenient chiral synthetic intermediates

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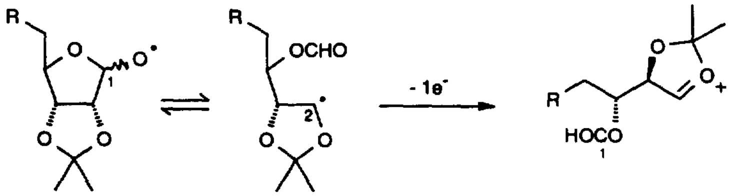
Abstract

A new procedure for the C1–C2 fragmentation of cyclic carbohydrates, through the formation of anomeric alkoxy radicals from the corresponding nitrate esters, with $^{n}Bu_3SnH$/azobisisobutyronitrile (AIBN), affords acyclic alditols in good yields. © 1998 Elsevier Science Ltd. All rights reserved.

Carbohydrates are important synthetic precursors to enantiomerically pure molecules because of their easy availability, well-defined stereochemistries, and highly functionalized structures.[1] Over the last few years, we have been engaged in developing methods for the β-fragmentation of glycopyran-1-*O*-yl and glycofuran-1-*O*-yl radicals with the aim of preparing chiral building blocks for the synthesis of complex molecules possessing multiple adjacent stereocenters.[2] We have shown that these alkoxy radicals can be obtained under mild oxidative conditions by the action of a (diacetoxyiodo)benzene/iodine system on the anomeric alcohol of monosaccharides, and that they undergo β-fragmentation reactions to give a C2 radical. This C-radical can be oxidized by the I(III) reagent to give an oxonium ion, which subsequently may be trapped inter- or intramolecularly to give different types of compounds (Eq. 1).[2]



(1)

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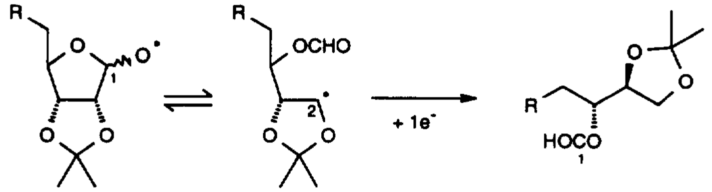


(2)

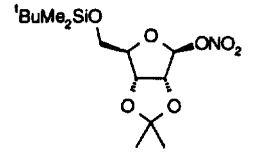
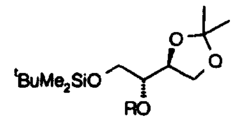
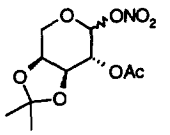
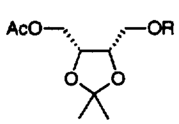
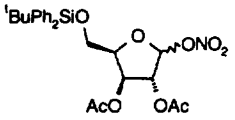
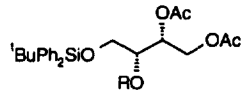
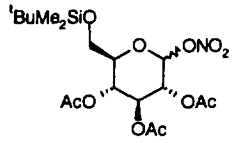
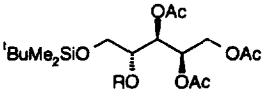
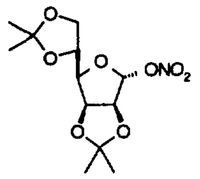
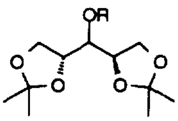
Herein we describe our attempts to prepare anomeric alkoxy radicals of carbohydrates under reductive conditions, as an alternative new strategy with different synthetic possibilities. We based our procedure on the formation of the nitrate ester of the anomeric alcohols as a suitable group to produce alkoxy radicals under reductive conditions.[2] Surprisingly, anomeric nitrate esters do not seem to have been previously synthesized by direct nitration of the alcohols. However, their preparation was accomplished by a slight modification of existing methodology for the nitration of alcohols.[3] The reaction of glycals with sodium azide in the presence of ceric ammonium nitrate to give nitrate glycosides of 2-azide sugars is the only reference to anomeric nitrates that we have found in the literature.[4] Anomeric nitrate esters are in most cases relatively stable compounds that can be purified by quick chromatography and stored in the refrigerator.

The reduction of nitrate esters[5] with $^{n}Bu_3SnH$/AIBN yields the corresponding anomeric alkoxy radicals, as proposed in Eq. 2, that under the reaction conditions undergo C1–C2 ring cleavage by β-scission and reduction of the formed C2 radical to give the corresponding nor-compounds in high yield. In this way alditols can be obtained with a variety of protective groups compatible with the reaction conditions. The scope of the reaction for the one carbon degradation was examined for pentoses and hexoses, as shown in Table 1.

Enantiomerically pure erythritol derivatives are important four-carbon chiral building blocks in natural product synthesis.[6] Therefore, we have prepared the nitrate derivatives of D-ribofuranosyl **1** and L-arabinopyranosyl **3** and used them to obtain D-erythritol derivatives **2** and **4** possessing very different patterns of protection in order to explore this methodology for the preparation of chiral synthons.[7] Nitrate **1**, a stable compound that was obtained in good yield (85%) by direct nitration of the corresponding anomeric alcohol, gave, under the reaction conditions shown in Table 1 (entry 1), the formate **2a** containing a small amount of the alcohol **2b** in 95% overall yield. If pyridine was omitted, the yield of the alcohol **2b** increased to 72% and only 17% of the formate **2a** was obtained. The β-fragmentation reaction also occurred with pure L-arabinopyranosyl nitrate **3** and a synthetically useful 4-*O*-acetyl-1-*O*-formyl-2,3-*O*-isopropylidene-D-erythritol **4a** was obtained in good yield (entry 2). Unfortunately, nitrate ester **3** was unstable and could not be purified by chromatography without substantial hydrolysis. When the reductive fragmentation was performed with the crude nitration reaction only 45% of the **4a–b** mixture was formed along with 33% of the starting alcohol 2-*O*-acetyl-3,4-*O*-isopropylidene-L-arabinopyranose. Threitol derivatives are also important four-carbon chiral synthons[8] so we have investigated the reduction of the D-xylofuranosyl nitrate **5** (entry 3). The D-threitol derivatives **6a–b** were obtained in good yield.

The reaction was also extended to carbohydrates of the hexose series (entries 4 and 5); thus D-glucopyranosyl nitrate **7** and D-mannofuranosyl nitrate **9** were transformed into the D-arabinitol derivatives **8a–b** and **10a–b**, respectively, in excellent yields. This is an example of the potential interest of this reaction; two D-arabinitol derivatives possessing very different protection patterns have been synthesized from simple accessible carbohydrates. The position of the readily hydrolyzable formate group only depends on the pyranose or furanose form of the starting carbohydrate and this feature may be of interest when the alditols need further transformations.

Table 1
Fragmentation of anomeric alkoxy radicals under reductive conditions

Entry	Substrate	Conditions[a]		Products	Yield
		$^{n}Bu_3SnH$ (mmol)	time (h)		
1	 **1** (85%)	9	4	 **2a** R = CHO b R = H	79 16
2	 **3**	6	0.5	 **4a** R = CHO b R = H	75 16
3	 **5** (56%)[b]	9	1.5	 **6a** R = CHO b R = H	58 16
4	 **7** (81%)	9	2	 **8a** R = CHO b R = H	83 12
5	 **9** (86%)[b]	7	2	 **10a** R = CHO b R = H	58 38

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[a] All reactions were performed in dry C_6H_6 (15 ml) at reflux temperature under nitrogen, containing $^{n}Bu_3SnH$ (as indicated), AIBN (0.1 mmol), and dry Py (1 mmol) per mmol of substrate. [b] Pyridine was omitted.

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7. Fuming HNO_3 (100%, 0.3 ml, 7 mmol) was added dropwise to Ac_2O (0.3 ml) at 0°C with stirring (CAUTION! Although these experiments have proceeded without incident, the combination of acetic anhydride and nitric acid, presumably leading to acetyl nitrate, can be hazardous and the reactions should be carried out in a hood behind a safety shield). The resulting mixture was added to a solution of the alcohol (1 mmol) in Ac_2O (0.6 ml) at 0°C and stirred at this temperature for 35–45 min. The solution was then poured into a mixture of CH_2Cl_2 and a saturated aqueous solution of $NaCO_3H$ at 0°C and extracted with CH_2Cl_2.
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