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Synthesis of alditols by reductive radical fragmentation of *N*-phthalimido glycosides. Preparation of chiral synthetic intermediates

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Abstract

The reaction of *N*-phthalimido glycofuranosides and glycopyranosides with $^{n}Bu_3SnH$/AIBN produces radical β-fragmentation of the carbohydrate C1–C2 bond through the formation of anomeric alkoxy radicals. This constitutes a new two-step methodology for the facile conversion of carbohydrates into the corresponding acyclic alditols with one fewer carbon.

In a previous paper from this laboratory we described a new methodology for the synthesis of acyclic alditols by C1–C2 fragmentation of carbohydrate anomeric nitrate esters.[1] The reaction proceeded under reductive conditions ($^{n}Bu_3SnH$/AIBN) through the formation of anomeric alkoxy radicals. Although the β-fragmentation reaction yields were generally high (74–98%), the formation of the anomeric nitrate esters suffered from a number of drawbacks: the mixture of fuming HNO_3 and acetic anhydride used in the nitration of the anomeric alcohols is not compatible with easily oxidised or highly acid-sensitive substrates. Unfortunately, many useful protective groups in carbohydrate chemistry fall into these categories (e.g. benzyl, *p*-methoxybenzyl, benzylidene and sensitive silyl ethers). A further problem with anomeric nitrates is that in some cases they have proved to be unstable and a substantial loss of material occurs during isolation and purification. This is the case of 2-*O*-acetyl-3,4-isopropylidene-L-arabinopyranose from which the interesting four-carbon chiral synthon 4-*O*-acetyl-1-*O*-2,3-isopropylidene-D-erythritol could only be obtained in 45% overall yield after the two steps, due to the instability of the nitrate ester.[1]

A more stable alkoxy radical precursor would be desirable. Therefore, an alternative and complementary approach to this methodology was explored using *N*-phthalimido glycosides. Kim et al.[2] have previously described that the reduction of *N*-alkoxyphthalimides with $^{n}Bu_3SnH$/AIBN gives alcohols and that the reaction proceeds through an alkoxy radical intermediate. On the other hand, *N*-

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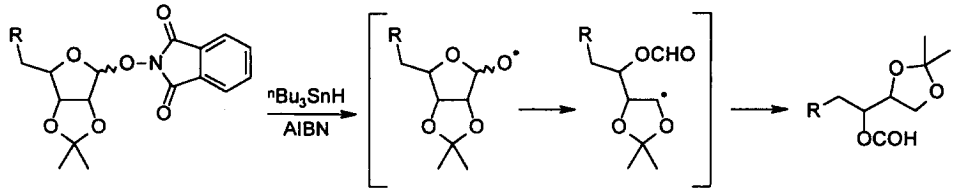
acyloxyphthalimides can be transformed into alkyl chlorides by photosensitised chlorodecarboxylation.[3] This procedure is based on the formation of a carboxyl radical that evolves CO_2 to give an alkyl radical that can be subsequently trapped by a halogen atom. Moreover, *N*-alkoxyphthalimides can be easily prepared by two general methods, from the corresponding alcohol and *N*-hydroxyphthalimide under Mitsunobu conditions,[4] and from alkyl halides by displacement with the sodium salt of *N*-hydroxyphthalimide.[2] In order to make the *N*-phthalimido glycosides we used the Mitsunobu protocol, as described by Grochowski and Jurczak.[4b,c] In our case the best results were accomplished using an excess of reagents (4 equiv.) at 0°C, according to the general procedure.[5] The generation of the alkoxy radicals was performed with $^{n}Bu_3SnH$/AIBN (Scheme 1) and the corresponding alditol derivatives were obtained under the conditions and in yields outlined in Table 1.[6]



Scheme 1.

We have prepared phthalimido glycosides from D-ribofuranose and L-arabinopyranose derivatives **1** and **3** in order to obtain erythritol derivatives **2** and **4** (Table 1, entries 1 and 2). The use of enantiomerically pure *meso*-erythritol derivatives that have become asymmetric by substitution has attracted considerable attention from synthetic chemists as four-carbon chiral synthons.[7] The overall yield of **2** is similar to the one obtained from the reduction of the corresponding nitrate ester but **4** could not be obtained in yields higher than 40% using this methodology.[1]

The reaction of the 2-deoxy-ribopyranose derivative **5** (entry 3) gave a volatile mixture of the expected alcohol and formate which was hydrolysed in situ with imidazole and subsequently treated with $^{t}BuPh_2SiCl$ to give the threitol derivative **6** in order not to lose material during the work-up and purification steps.

N-Phthalimido D-glucosides derivatives **7** and **9** were synthesised in view of the fact that attempted preparation of its corresponding anomeric nitrate ester failed completely. Tetra-*O*-benzyl-D-arabinitol **8** was obtained in good yield but 1-acetamido-2,4,5-tri-*O*-acetyl-1-D-arabinitol (**10**) only in 47% yield (entries 4 and 5). Interestingly, the formation of compound **10** could only be rationalised by admitting complete hydrolysis of formate and intramolecular transesterification from the acetate at C-3 to the alcohol at C-4.[8] These facts may account for the observed low yield.

Studies directed toward the inter- and intramolecular trapping of the C-2 radical are currently in progress and will be reported in due course.

Acknowledgements

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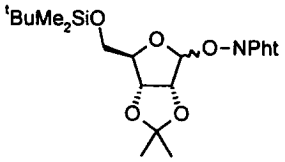
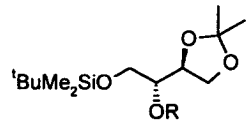
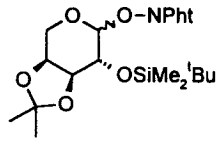
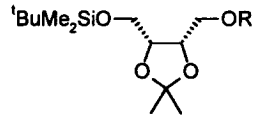
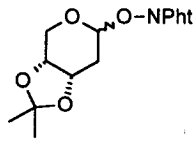
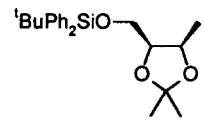
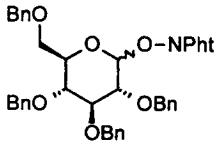
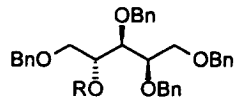
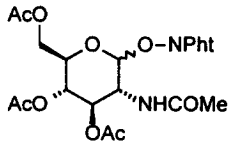
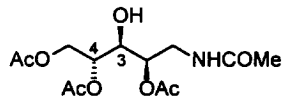
Table 1
Fragmentation of *N*-phthalimido glycosides under reductive conditions[a]

Entry	Substrate	Time (min)	Products	Yield (%)
1	 **1** (97%)	30	 **2a** R = CHO **2b** R = H	42 39
2	 **3** (81%)	30	 **4a** R = CHO **4b** R = H	64 31
3	 **5** (54%)	35	 **6**[b]	78
4	 **7** (69%)	30	 **8a** R = CHO **8b** R = H	63 23
5	 **9** (72%)	240	 **10**	47

[a]All reactions were performed in dry C_6H_6 (15 ml) at reflux temperature under nitrogen, containing $^nBu_3SnH$ (9 mmol), AIBN (0.1 mmol) per mmol of substrate. [b]To the reaction mixture was added imidazole (2 mmol) and stirred at 80 °C for 1.5 h. After this the reaction was cooled to r.t. and more imidazole (4 mmol) and $^tBuPh_2SiCl$ (2 mmol) were added and stirred for 1h at this temperature. PhtN– = Phthalimido.

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Grochowski, E. In *International Symposium on Phosphorus Chemistry Directed Towards Biology*, Burzenin, Poland, 1979; Stec, W. J., Ed.; Franklin Book Company, 1980; p. 54.

5. General procedure for the preparation of *N*-phthalimido glycosides: To a stirred solution of the carbohydrate (1 mmol) in dry THF (10 ml) were added, under nitrogen, *N*-hydroxyphthalimide (4 mmol) and triphenylphosphine (4 mmol) and cooled to 0°C. Then diethylazodicarboxylate (4 mmol) was added dropwise and the solution was stirred at this temperature for 1 h. The reaction mixture was poured into water and extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatotron chromatography was used to purify the residue.
6. General procedure for the reduction of *N*-phthalimido glycosides: To a solution of glycoside (1 mmol) in dry benzene (15 ml) were added, under nitrogen, tributyltin hydride (9 mmol) and AIBN (0.1 mmol). The mixture was stirred at reflux temperature for the period of time stated in Table 1 and concentrated. The residue was dissolved in CH_3CN, washed with *n*-hexane and concentrated under reduced pressure. Chromatotron chromatography was used to purify the residue.
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8. A similar transesterification has been observed during the hydrolysis of 1,2,3-tri-*O*-acetyl-5-*O*-(*tert*-butyldimethyl)silyl-4-*O*-formyl-D-arabinitol synthesised in Ref. 1.