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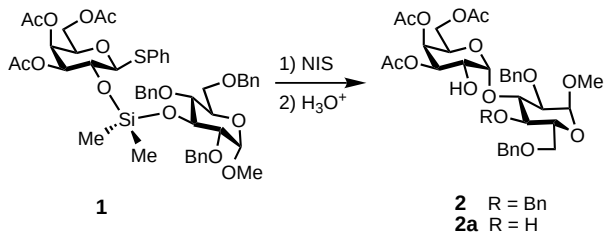
A New Intramolecular Reaction for the Regioselective Debenzylation or Protection of Alcohols**

Jacob Madsen and Mikael Bols*

In an earlier study of silicon-tethered intramolecular glycosidation reactions it was observed that treatment of compound **1** with *N*-iodosuccinimide (NIS) gave both the expected glycoside **2** and an unexpected debenzylated product **2a** (Scheme 1).[1] Originally we believed that this debenzylation reaction followed an intramolecular pathway involving silicon during the glycosidation procedure. We came to this conclusion for two reasons: The reaction was regioselective, and if the reaction mixture was not treated with acid after the glycosidation, a debenzylated, silicon-bridged product was isolated (Figure 1).[1a]



Scheme 1. Intramolecular glycosidation with formation of two products. Bn = benzyl.

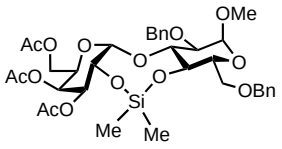


Figure 1. Compound isolated when the reaction mixture from Scheme 1 was not treated with acid.

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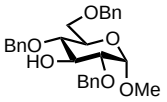
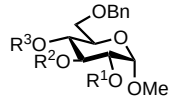
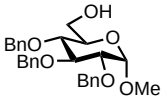
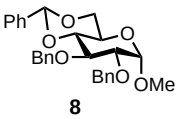
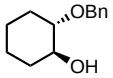
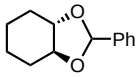
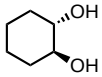
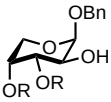
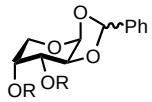
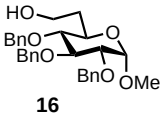
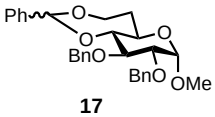
[**] We thank the Danish National Research Council for financial support (grant no. 9502986).

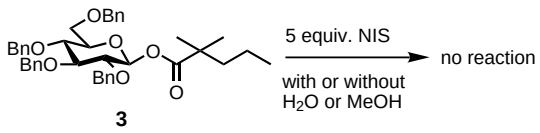
We have now reinvestigated the reaction (Scheme 1) and have come to the conclusion that the debenzylation apparently is not connected to the glycosidation process. In fact treatment of compound **2** with NIS in $MeNO_2$ gave compound **2a** (Table 1). This indicated an intermolecular reaction and indeed no participation by silicon. On the other hand the regioselectivity of the debenzylation suggested an intramolecular reaction and in that case the only possibility seemed to be participation of the free OH group at C-2 in the galactose unit.

Table 1. Reaction of benzylated compounds containing free OH groups with NIS.[11]

Reactant	Product	Solvent/Equiv. NIS	Yield [%]
2	**2a**	$MeNO_2$/2.5	36[a]
 **4**	 **5** R^1 = Bn, R^2 = R^3 = H **6** R^1 = R^2 = H, R^3 = Bn	$MeNO_2$/2.5[b]	80 (32) (48)
 **7**	 **8**	$MeNO_2$/5[c]	74
 **9**	 **10**	CH_2Cl_2/2.5[d]	49
9	 **11**	CH_2Cl_2/2.5[b, d]	66
 **12** R = H **14** R, R = CMe_2	 **13** R = H **15** R, R = CMe_2	CH_3CN/5	41 – 44
 **16**	 **17**	$MeNO_2$/5	84

[a] Not optimized. The crude product was a 2:1 mixture of **2** and **2a**, respectively, so the recovered yield was very high. [b] Treatment with TFA/H_2O 5/1. [c] Reaction with 20 equiv NIS gave **8** in 76% yield. [d] Reaction at room temperature.

The presence of the unprotected alcohol was found to be essential. When glucose derivative **3**[2] (Scheme 2) was treated with NIS (5 equiv), no reaction was observed even on addition of water or methanol. In contrast, when readily available alcohol **4**[3] was refluxed for 2 h in $MeNO_2$ with NIS (2.5 equiv) quantitative conversion to less polar products was observed (by thin-layer chromatography) with simultaneous formation of iodine (Table 1). These products could not be purified by chromatography due to their instability, but on



Scheme 2. Without an unprotected alcohol present in the molecule no reaction occurred.

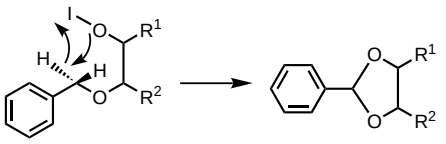
hydrolysis of the reaction products with TFA/H_2O 5/1 the two diols **5** and **6** were isolated in 32% and 48% yield, respectively (total yield: 80%). Compound **5** was identified by comparison with the known spectrum,[4] compound **6** by conversion to the diacetate.

The initially formed less polar products were assumed to be 1,2-*trans* benzylidene derivatives, which would account for the instability. To confirm the formation of a benzylidene derivative, compound **7**[5] was treated with NIS (5 equiv). This gave the anticipated product **8** in 74% yield.

We also investigated a compound of non-carbohydrate structure. Alcohol **9**[6] reacted with NIS (5 equiv) to give the new *trans*-benzylidene compound **10**[7] in 49% yield. ^{1}H and ^{13}C NMR and EI mass spectral data as well as the lower retention time of **10** than **9** on silica gel supported the proposed structure and configuration of **10**. Unlike the corresponding *cis*-benzylidene compound[8] the symmetry of **10** only allows formation of one stereoisomer at the benzylidene center; this exhibits different chemical shifts for all carbon and hydrogen atoms. The atoms H-1 and H-2 of **10** have slightly different chemical shifts but identical coupling constants. Furthermore these two H atoms display two large coupling constants, which were consistent with the protons being axial. The ^{1}H NMR spectra of **10** and its *cis* isomer[8] are very similar except that the signals of H-1 and H-2 lie between $\delta = 3.39 - 3.47$ in **10** and between $\delta = 3.99 - 4.3$ in the *cis* compound.[8] This also confirmed the axial position of H-1 and H-2 in **10**. The lower yield in this case was not a result of a low degree of debenzylation, but rather instability of **10** under the conditions of the reaction and isolation. Thus if in a similar experiment the reaction mixture was subjected to hydrolytic work-up diol **11** could be isolated in 66% yield.

Further examples of this new reaction, which appears to be generally applicable, are given in Table 1. Benzyl-β-D-arabinopyranoside **12**[9] and benzyl-3,4-isopropylidene-β-D-arabinopyranoside **14**[10] gave the expected acetals **13** and **15** in 44% and 41% yield, respectively. Again instability of the benzylidene compounds accounts for the diminished yields. Particularly noteworthy is the reaction of **12** because it is an example of a selective protection of a hydroxyl group vicinal to a benzyl ether. Interesting is also the conversion of compound **16**[10] to benzylidene derivative **17** in 84% yield as it results in the formation of a seven-membered ring.

The reaction occurs in a variety of solvents (MeCN, $MeNO_2$, CH_2Cl_2) with no large difference in rate. In general NIS is used in the reaction in stoichiometric amounts (2 equiv), but frequently several extra equivalents were necessary to ensure complete conversion. The mechanism of the reaction is probably ionic, as addition of 2,2′-azobisisobutronitrile (AIBN) did not favor the reaction; nor could NIS be substituted with *N*-bromosuccinimide. Since the reaction only occurs at benzyl groups vicinal to a hydroxyl group we suggest that the OH group participates in the reaction in the manner proposed in Scheme 3. Reaction between the hydroxyl group and NIS leads to formation of a hypoiodite that abstracts a proton from the neighboring benzyl group leading to a benzylidene group.



Scheme 3. Suggested mechanism for the formation of benzylidene derivatives.

Finally one may wonder why this reaction had not been detected previously as it would be expected to occur at least to some extent in NIS-promoted glycosidation of many benzylated glycosyl acceptors. In fact Hindsgaul et al. have observed the formation of **8** as a by-product in NIS-catalyzed tethered glycosidations which may well have been formed from **7**.[12]

In conclusion we have presented a new reaction that has considerable potential for selective reactions of polyfunctional alcohols or benzyl ethers and that should facilitate protection group chemistry. NIS very efficiently promotes debenzylation of monobenzylated 1,2-, 1,3-, and 1,4-diols and in many cases the intermediate benzylidene derivatives can be isolated.

Received: April 30, 1998 [Z11798IE]
German version: *Angew. Chem.* **1998**, *110*, 3348 – 3350

Keywords: acetals · carbohydrates · protecting groups

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