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A practical approach to regioselective O-benzylation of primary positions of polyols

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ABSTRACT

Exposure of saccharide polyols to a moderate excess of benzyl bromide and DIPEA at 90 °C results in the regioselective O-benzylation of primary positions in moderate to good yields. The reactions can be performed without inert atmosphere and provide synthetically useful yields within a few hours.

Benzylation represents one of the most popular approaches to the protection of alcohols in organic synthesis. This is due to the compatibility of the resulting benzyl ethers to a wide range of chemical conditions as well as the mild conditions for their cleavage.[1] In this regard, an especially intriguing problem is the selective installation of benzyl protecting groups on synthetically relevant polyol substrates such as carbohydrates. The straightforward differentiation of similar functionalities is indeed a critical issue addressed by numerous synthetic efforts.

The most applied strategy for the selective installation of benzyl groups on carbohydrate polyols relies on the in situ generation of reactive stannylidene or stannyl ether intermediates and their subsequent exposure to benzyl bromide.[2] This sequence suffers from the use of stoichiometric amounts of toxic tin reagents. Sparse examples of alternative approaches based on the stoichiometric generation of copper,[3,4] mercury,[4] and nickel[5] complexes have been reported in the literature. To alleviate the issue of the need for stoichiometric amounts of toxic reagents, some attempts have been made to develop catalytic approaches. In this regard, the combination of catalytic amounts of suitable borinic acids with stoichiometric Ag_2O was found effective to carry out a wide range of regioselective protections, including benzylations.[6] In a few examples of an alternative strategy where preliminary generation of complexes is avoided, the combination of excess Ag_2CO_3 and benzyl bromide in toluene resulted in a faster benzylation at primary positions of saccharide polyols, but the process was totally inhibited when disarming acyl protecting groups were adjacent to the primary carbinol.[7] On the other hand, a closer inspection of the available procedures for regioselective O-benzylations reveals that the selective protection of primary carbinol positions is not necessarily the favorite pathway as generally observed for alternative protecting groups.[8] For example, glycosides of D-*manno* and D-*galacto* compounds are known to be preferentially benzylated at *O*-3 when stannylidene intermediates are exploited.[9] In addition, the borinic acid based protocol was described to yield a mixture of products when applied to sugars with a free primary alcohol.[6] On the other hand an approach for regioselective 6-O-benzylation of glucose derivatives based on the use of excess amounts of a strong base such as sodium hydride was recently reported.[10]

Spurred by our long term interest toward the development of practical procedures for regioselective modification of carbohydrates,[11–14] we have developed the procedure herein reported to carry out the regioselective benzylation of primary positions of carbohydrates. The procedure was inspired by a very interesting approach recently reported by Maki and co-workers for the benzylation of alcohols.[15] In that paper it was shown that primary and secondary alcohols can be O-benzylated at a temperature as high as 150 °C in the presence of nearly equimolar amounts of DIPEA and benzyl bromide and in the absence of any solvent. The protocol was also successfully applied to the di-O-benzylation of a saccharide diol (with addition of catalytic NaI) and displayed compatibility with base labile ester groups. Due to the avoided use of high boiling and toxic DMF solvent, that protocol looked very attractive and was thereby examined by us for the attempted benzylation of sugars bearing more than two free carbinol positions. On assessing the reactivity of several sugars we noted that at 90 °C the benzylation

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of saccharide primary carbinols occurred at an appreciable rate in the presence of equimolar amounts of DIPEA and benzyl bromide.

In order to optimize the procedure model triol **1** was initially exposed to benzyl bromide and DIPEA (4 equiv both) at 90 °C in the absence or in the presence of additives (Table 1). Consistent with the above mentioned paper by Maki and co-workers,[15] substoichiometric NaI had a beneficial effect on the yield (Table 1, entry 2). Use of TBAI as an alternative additive resulted in a very similar yield but in a shorter reaction time (compare entries 3 and 2). Another slight improvement was eventually recorded by performing the reaction in the presence of substoichiometric TBAI with two sequential additions of benzyl bromide and DIPEA (2 equiv) (entry 4) instead of adding the whole amount of both reagents since the beginning of the reaction. It should be noted at this stage that all the experiments herein reported were performed under air, and the procedure was thereby experimentally very easy. In addition, the yield reported in entry 4 was found to be reproducible at a gram scale.

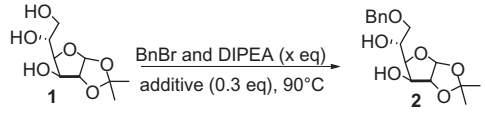
Interestingly, attempted application of analogous conditions with a more reactive electrophile such as *p*-methoxybenzyl chloride resulted in a lower regioselectivity.[16]

After the preliminary screening of conditions for selective O-benzylation, the best performing protocol based on the portion-wise addition of DIPEA and benzyl bromide (Table 1, entry 4) was then assessed with several polyols as shown in Table 2.

Attempted O-benzylation of pyranoside 3,4,6-triols **3** and **5** (Table 2, entries 2 and 3) provided the corresponding 6-O-benzylated products **4** and **6** in satisfying yields (56% and 64%, respectively) within relatively short times (6–7 h). For comparison, the more laborious conversion of **5**–**6** via a stannyl ether intermediate was described to proceed in ca. 20 h with a slightly higher yield (71%).[17] 6-O-Benzylation of 4,6-diol **7** proceeded in a good yield (61%) and an almost quantitative conversion into **8** (entry 4) upon use of 6 equiv of DIPEA and BnBr (in three portion-wise additions); the presence of strong electron withdrawing benzoyl groups likely accounts for the lower reactivity of **7** that is also evidenced by its recovery in significant amounts (35%). As mentioned above, this kind of disarming effect was previously also observed in other mild benzylation procedures.[7]

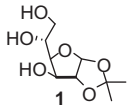
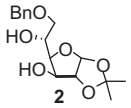
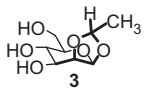
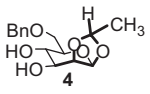
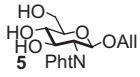
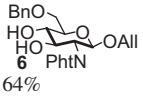
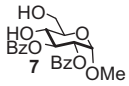
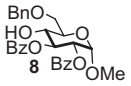
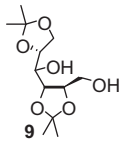
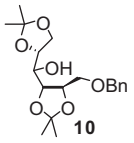
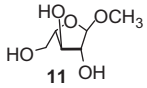
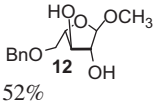
The procedure proved also effective when applied to a distal diol contained in an acyclic chain such as the mannitol model derivative **9**. In particular, comparison of results in entries 5 and 6 in Table 2 confirms that the protocol based on the portion-wise addition of reagents (entry 6) provides the product benzylated at the primary position in a higher yield (74% and 61% yield for entries 6 and 5, respectively). For comparison, a previously reported procedure for the regioselective protection of the same diol was described to proceed in 70% yield upon overnight exposure of the substrate to a moderate excess of Ag_2O and BnBr.[18] In entry 7 is also shown the feasible selective 5-O-benzylation in a satisfying yield of a model pentose furanoside compound, such as L-arabinoside **11**.

Table 1
Regioselective O-benzylation of **1**



Entry	Equiv of BnBr and DIPEA (time)	Additive	Isolated yield of **2** (%)
1	4 (6 h)	None	62
2	4 (7.5 h)	NaI	70
3	4 (5.5 h)	TBAI	68
4	2 (4 h) and 2 (2 h)	TBAI	76

Table 2
Regioselective primary O-benzylation of saccharide polyols

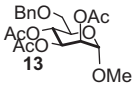
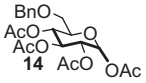
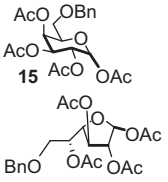
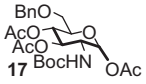
Entry	Reagent	Products and yield (conversion)
1	 **1**	 **2** 76%
2	 **3**	 **4** 56%
3	 **5** PhtN	 **6** PhtN 64%
4[a]	 **7**	 **8** 61% (94%)
5[b]	 **9**	 **10** 63%
6	**9**	**10** 74%
7	 **11**	 **12** 52%

General conditions: TBAI (0.3 equiv), DIPEA and BnBr (2 equiv), 90 °C, 4 h; then addition of further DIPEA and BnBr (2 equiv), 2–5 h.
[a] Further addition of DIPEA and BnBr (2 equiv, 6 overall equiv) after 6 h.
[b] 4 equiv of DIPEA and BnBr added since the beginning of the reaction.

The proposed approach was found synthetically useful even with some polyols bearing more than three hydroxyl groups. In these cases the recovery of products was simplified by adding an in situ acetylation step that was performed by further addition of DIPEA and acetic anhydride to the benzylation vessel. For example, methyl α-mannopyranoside was converted into 6-O-benzylated derivative **13** (acetylated at secondary positions) in a good overall yield (Table 3, entry 1). Even more interesting was the feasible application of the method to some aldoses in a reducing form as evidenced by examples in entries 2–4 of Table 3. Application to D-glucose provided pyranoside **14** in a moderate overall 36% yield (Table 3, entry 2) that is indeed a result of synthetic relevance in view of the difficult direct access to the same building-block by alternative pathways. Interestingly, the application of the same protocol to D-galactose provided a mixture of inseparable furanoside and pyranoside species **15** and **16** in comparable amounts, both still evidencing the high regioselectivity of the benzylation step (Table 3, entry 3). An especially good result was observed on applying the protocol to commercially available *N*-Boc glucosamine, with the final isolation of pure 6-O-benzylated product **17** in 54% isolated yield (Table 3, entry 4). Interestingly, the starting product was almost quantitatively recovered in a per-O-acetylated form to indicate a very high conversion in the benzylation step (Table 3, entry 4).

In conclusion in this Letter we have shown that simple use of a moderate excess of DIPEA and benzyl bromide and substoichiometric TBAI at 90 °C can affect the regioselective benzylation of

Table 3
Sequential regioselective O-benzylation/per-O-acetylation of saccharide sugars in a reducing form

Entry	Reagent	Products and yield (conversion)[a]
1	Methyl D-*manno* pyranoside	 **13** 51%
2	D-Glucose	 **14** 36%
3	D-Galactose	 **15**+**16**: 44%
4	*N*-Boc glucosamine	 **17** 54 (92 %)

General conditions: TBAI (0.3 equiv), DIPEA and BnBr (2 equiv), 90 °C, 4 h; then addition of further DIPEA and BnBr (2 equiv), 2 h (for entry 1) or 5 h (for entries 2–4); then addition of DIPEA (4 equiv) and acetic anhydride (6 equiv), overnight at rt.
[a] The conversion refers to the recovery of starting material in a per-O-acetylated form.

primary carbinols within a few hours.[19] The protocol appears practically very convenient in that reactions can be performed without any solvent and without resorting to inert atmosphere conditions. In addition, unlike other reported procedures, the proposed protocol does not entail preliminary polyol activation via generation of metal complexes, neither the use of excess amounts of expensive silver salts.

Acknowledgment

NMR and MS facilities of CIMCF ('Centro Interdipartimentale di Metodologie Chimico-Fisiche dell'Università di Napoli') are acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.023.

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16. Exposure of **1** to 2 equiv of *p*-methoxybenzyl chloride and DIPEA at 90 °C (and no additive) provided a ca. 3:1 mixture of inseparable 6-*O*- and 5-*O*-PMB regioisomers (ca. 55% combined yield).
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18. Shen, X.; Wu, Y.-L.; Wu, Y. *Helv. Chem. Acta* **2000**, *83*, 943–953.
19. *General procedure for regioselective benzylation*: to a vessel containing the polyol (1 mmol) and TBAI (111 mg, 0.3 mmol) were sequentially added DIPEA (0.34 mL, 2 mmol) and benzyl bromide (0.24 mL, 2 mmol). The vessel was placed on an oil bath at 90 °C. After 4 h a further aliquot of DIPEA and benzyl bromide (2 equiv both) was added. The vessel was kept at 90 °C for the times indicated in the tables, then the mixture was diluted with dichloromethane and the organic phase washed with water. Aqueous phase was re-extracted with dichloromethane and collected organic phases were dried and concentrated in vacuo. The residue was purified by silica-gel flash chromatography (eluent: hexane/ethyl acetate mixtures). *General procedure for regioselective benzylation and* 'in situ' *acetylation*: upon completion of the benzylation step (see procedure above described) the reaction vessel was cooled to rt and then DIPEA (0.68 mL, 4 equiv) and acetic anhydride (0.60 mL, 6 equiv) were sequentially added. After 2–3 h (overnight stirring was occasionally applied for convenience) the mixture was treated with methanol at 0 °C and then submitted to the analogous extractive work-up and purification procedures described above.