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Facile cleavage of carbohydrate benzyl ethers and benzylidene acetals using the $NaBrO_3/Na_2S_2O_4$ reagent under two-phase conditions

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Abstract

Benzyl ether and benzylidene acetal carbohydrate protecting groups can be selectively cleaved by reaction with sodium bromate/sodium dithionite in ethyl acetate/water. Under the mild (room temperature, short reaction time) conditions needed, a variety of other protecting functionalities such as acetyl, chloroacetyl, benzoyl, pivaloyl, tosyl, *t*-butyldimethylsilyl, trityl, and isopropylidene groups remain unaffected.

Keywords: cleavage reactions; carbohydrates.

Benzyl ethers are widely used in organic synthesis for the protection of hydroxyl groups because of their tolerance to a wide range of chemical conditions. These versatile *O*-protecting groups, among the most useful in carbohydrate chemistry, are typically removed with Pd/C (or $Pd(OH)_2/C$) with hydrogen,[1–3] by catalytic transfer hydrogenation using formic acid[4] or other reagents[3,5,6] as suitable sources of hydrogen, or in the presence of strong Lewis acids, such as $BF_3 \cdot OEt_2$ (in combination with sulfur nucleophiles),[7] strictly anhydrous $FeCl_3$,[8,9] TMSI[10] etc. Furthermore, the deprotection can be performed under strongly basic conditions with sodium or lithium in ammonia.[11,12] Debenzylation can also be performed under UV irradiation by using NBS/H_2O through a reaction pathway presumably involving radical bromination at the benzylic position and subsequent hydrolysis of the resulting α-bromo ether.[13]

An interesting approach for the selective mono α-bromination of alkyl benzenes based on the combined use of $NaBrO_3$ and a suitable reducing reagent (such as $NaHSO_3$) under two-phase conditions has recently appeared in the literature.[14] The proposed mechanism contemplates the gradual decomposition of the formed HBrO in aqueous solution with liberation of Br· which moves to the organic phase and brominates the side-chain of the dissolved arene. Due to our interest in carbohydrate chemistry, we envisaged that such a reaction could be usefully exploited for the removal of benzyl protecting groups

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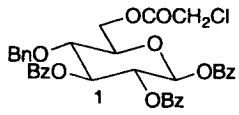
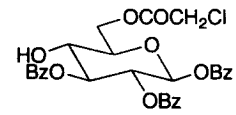
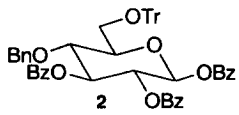
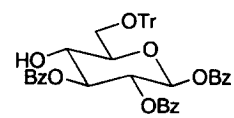
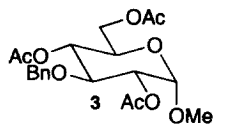
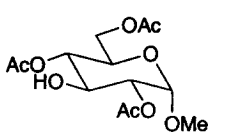
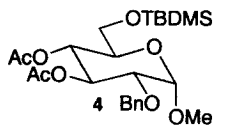
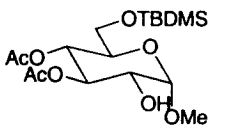
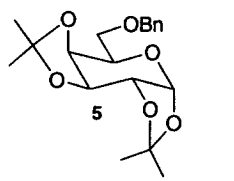
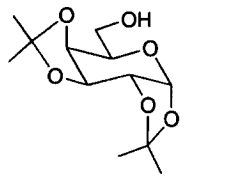
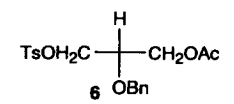
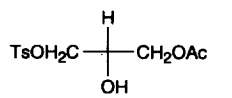
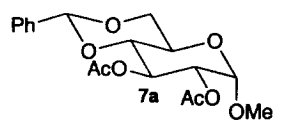
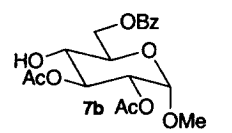
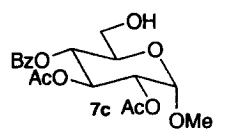
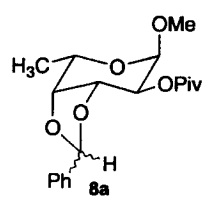
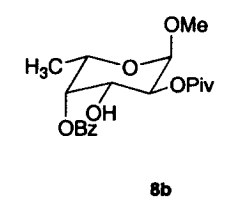
Table 1
Cleavage of benzyl and benzylidene carbohydrate protecting groups

Entry	Reagent	Products[a]	Time	Yield
1			3h	82%
2			6h	85%
3			3h	96%
4			3h	78%
5			1.5h	97%[b]
6			2h	73%
7		 	1.5h	88% **7b/7c**=35/65
8			1h	92%[c]

[a] Satisfactory spectral data were obtained for all products. [b] With $NaHSO_3$: time 2h, yield 95%. [c] With $NaHSO_3$: time 1h, yield 80%.

from sugar substrates. As a matter of fact we have found that the use of $NaBrO_3$ and sodium dithionite ($Na_2S_2O_4$) in ethyl acetate/water at room temperature is particularly effective for the fast and clean deprotection of several benzylated monosaccharides (Table 1, entries 1–6).[15]

Various functionalities such as esters, silyl, trityl ethers, acetonides and tosylates commonly employed for the derivatization of sugars, survived unaffected under the reaction conditions.

The propensity of cyclic benzylidenes to give benzylic bromination and subsequent oxidative opening with NBS/H_2O under UV or thermal activation is well known.[16] Therefore, we tested the $NaBrO_3/Na_2S_2O_4$ procedure to perform that transformation. The six-membered cyclic 4,6-*O*-benzylidene derivative **7a** was converted to a mixture of the 6-*O*- and 4-*O*-benzoyl regioisomers **7b** and **7c**, in high yield but with low regioselectivity (35:65).[17] On the other hand, the five-membered benzylidene **8a** was converted into the single axial 4-*O*-benzoyl isomer **8b**. Interestingly, the use of $NaBrO_3/Na_2S_2O_4$ required shorter reaction times and resulted in higher yields than the NBS/H_2O/UV procedure.[16]

In a typical procedure the benzylated (or benzylidene) sugar (0.3 mmol) was dissolved in ethyl acetate (4 mL) and then a solution of $NaBrO_3$ (136 mg, 0.9 mmol) in water (3 mL) was added. To the well stirred two-phase system an aqueous solution of $Na_2S_2O_4$ (85% pure, 157 mg, dissolved in 6 mL water) was added dropwise over 10 min at room temperature. After completion of the reaction (TLC) the mixture was diluted with EtOAc and the organic phase was washed with aq. sodium thiosulfate. The crude product was then purified by silica gel chromatography. With $NaHSO_3$ in place of $Na_2S_2O_4$ slightly lower yields were observed (entries 5 and 8).

In conclusion we have shown that the use of the $NaBrO_3/Na_2S_2O_4$ system can be a valuable alternative approach for the deprotection of benzyl ethers due to the mildness, cheapness, and experimental simplicity of the procedure.

Acknowledgements

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