ChemComm

This article is part of the

Glycochemistry & glycobiology web themed issue

Guest Editors are Professor Peter H. Seeberger and Dr Daniel B. Werz

Please visit the website to access the other articles in this issue:-
http://www.rsc.org/chemcomm/glycochemistry

ChemComm

Dynamic Article Links

Cite this: *Chem. Commun.*, 2011, **47**, 10485–10487

www.rsc.org/chemcomm

COMMUNICATION

Selective oxidative debenzylation of mono- and oligosaccharides in the presence of azides†‡§

Mathäus Niemietz, Lukas Perkams, Joanna Hoffman, Steffen Eller and Carlo Unverzagt*

Received 29th June 2011, Accepted 29th July 2011
DOI: 10.1039/c1cc13884g

When using benzyl ethers as permanent protecting groups in oligosaccharide synthesis selective oxidative debenzylation with $NaBrO_3$ + $Na_2S_2O_4$ under biphasic conditions is efficient and compatible with anomeric azides and many other functions.

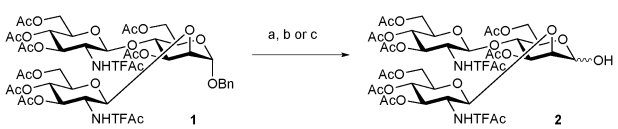
Azido groups on carbohydrates[1] are frequently used in the synthesis of glycoconjugates[2] by 1,3-dipolar cycloadditions[3] and in amide forming reactions *via* Staudinger ligation,[4] thioacids[5] or after reduction to an amine.[6] The introduction of azido groups can be carried out with protected sugars[7] but also on free carbohydrates at the anomeric center[8,9] or by diazotransfer to amino groups.[10] When using synthetic carbohydrates carrying temporary benzyl protection, azido groups need to be reacted prior to reductive debenzylation. Thus, a method for the selective removal of benzyl ethers in the presence of azides would be desirable. We found that a biphasic system using a combination of sodium bromate and sodium dithionite allows the selective cleavage of benzyl groups even in the presence of anomeric azides.

The appropriate use of permanent and transient protection groups is one of the key requirements of chemical oligosaccharide synthesis. Protecting groups control the overall reactivity of the building blocks as well as the stereochemistry during glycosylations.[11] Typically a complex combination of protecting groups is applied providing selective options for cleavage under acidic or basic conditions in conjunction with additional groups susceptible to reducing or oxidative environments. Benzylethers are frequently installed as permanent protecting groups due to their high stability towards acids and bases and are commonly removed using a variety of reducing conditions.[12] However, azides are more susceptible to reduction than benzyl groups. In order to combine the convenient use of stable benzyl protection during synthesis with the option to obtain azides after deprotection, non-reducing conditions are required. We thus investigated the selective cleavage of benzyl ethers in complex carbohydrates by Lewis acids and oxidative methods.[12]

For an initial screen on selective debenzylation methods we selected trisaccharide **1**[13] where the removal of the benzyl ether using Pd–H_2 in MeOH tended to be sluggish and consumed inadequate amounts of expensive catalyst. Dimethyldioxyrane (DMDO) was shown to cleave benzyl ethers[14] and thus **1** was reacted with DMDO (5 equiv.) in acetone.[15] The desired anomeric debenzylation was found, albeit only low conversion occurred. The acetyl and trifluoroacetamido groups were not affected under these conditions. Anhydrous $FeCl_3$ in DCM[16] at 0 °C was tested subsequently. It was found that 40 equivalents of $FeCl_3$ were required in order to convert most of trisaccharide **1** to the corresponding hemiacetal **2**. The addition of molecular sieves did not improve the conversion but instead more $FeCl_3$ was needed. By adding dry $FeCl_3$ in two portions an isolated yield of 85% of **2** could be obtained (Scheme 1).

We then tested biphasic oxidative debenzylation conditions,[17] which were adapted previously to carbohydrates by using $NaBrO_3/Na_2S_2O_4$.[18] Trisaccharide **1** was dissolved in ethyl acetate and stirred vigorously with an aqueous solution of $NaBrO_3$ and $Na_2S_2O_4$. High conversion occurred on a 2 g scale and after quenching the reaction with sodium thiosulphate the desired hemiacetal **2** was isolated in 91% yield next to only some unreacted starting material. Under the biphasic conditions the reaction appears to follow the proposed radical mechanism.[17] No evidence was found for any oxidation of the hydroxyl group, which may occur under certain conditions.[19]

Encouraged by this outcome the compatibility of the oxidative reagents with azides was tested. Azide **3**[20] was reacted with DMDO or $NaBrO_3/Na_2S_2O_4$. Under both conditions azide **3** was completely stable (Scheme 2). Subsequently, the regioselectivity for benzyl groups[21] was probed with the dibenzylated azide **4**.[22] In the case of DMDO two products were obtained. The major product **5**[23] (56% yield)



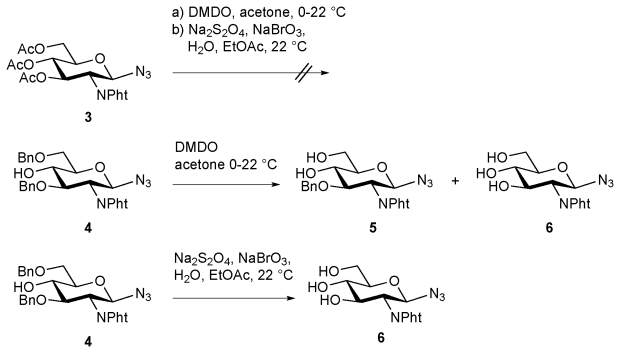
Scheme 1 (a) DMDO, acetone 0–22 °C (yield not determined); (b) $FeCl_3$, DCM, 0 °C (85%); (c) $Na_2S_2O_4$, $NaBrO_3$, H_2O, EtOAc, 22 °C (91%).

Bioorganische Chemie, Gebäude NWI, Universität Bayreuth, 95440 Bayreuth, Germany. E-mail: carlo.unverzagt@uni-bayreuth.de; Fax: +49-921-555365; Tel: +49-921-552670

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc13884g

‡ This work is dedicated to Prof. Gerhard Bringmann on the occasion of his 60th birthday.

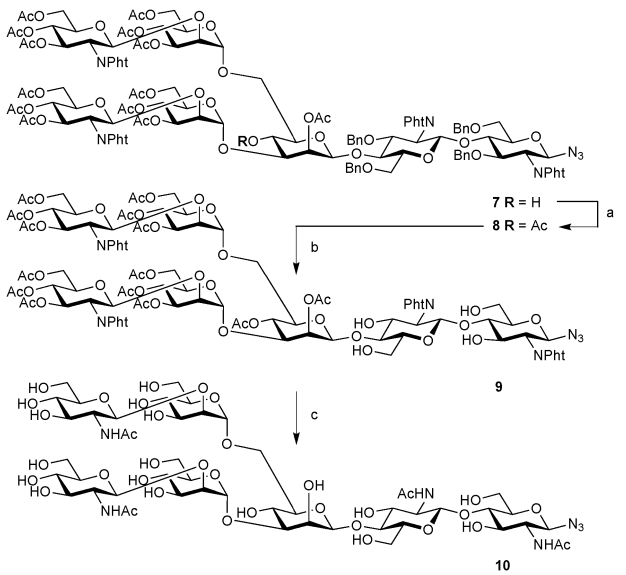
§ This article is part of the ChemComm 'Glycochemistry and glycobiology' web themed issue.



Scheme 2 Different selectivity of oxidative cleavage reagents for benzyl groups.

resulted from debenzylation only at the primary O-6 position whereas the minor product **6**[24] (20%) was completely debenzylated. A corresponding compound with a single debenzylation at O-3 was not detected after flash chromatography. The reaction of **4** with $NaBrO_3/Na_2S_2O_4$ gave complete conversion to the fully debenzylated product **6** as judged by TLC. Due to its high water solubility compound **6** migrated to the aqueous phase and was difficult to isolate. It was then investigated if non-anomeric azides are also compatible. When submitting peracetylated 2-azidoglucose to $NaBrO_3/Na_2S_2O_4$ no conversion occurred according to TLC and LC-MS, which indicated that the most common types of sugar azides are well tolerated.

For oxidative debenzylations the biphasic $NaBrO_3/Na_2S_2O_4$ system showed reliable and high conversions. The debenzylation of the biantennary N-glycan azide **8** was tested under these conditions. Heptasaccharide **8** was obtained from **7**[25,26] by acetylation. After stirring for 3.5 h at room temperature the reaction was complete and the debenzylated heptasaccharide azide **9** was obtained in 97% yield after flash chromatography. In order to probe the occurrence of side reactions with this



Scheme 3 Oxidative cleavage of multiple benzyl groups in a tetra benzylated complex N-glycan: (a) Ac_2O, pyridine; (b) $Na_2S_2O_4$, $NaBrO_3$, H_2O, EtOAc, 22 °C (97%); (c) 1. ethylene diamine, nBuOH, 90 °C; 2. Ac_2O, MeOH, H_2O (1.-2. 73%).

complex substrate (**9**), in particular the subsequent oxidation[19] of the liberated OH groups, we extended the reaction time to several days. To our delight only traces of a heptasaccharide, where the azido group was hydrolysed, were detectable by LC-MS. Presumably the acidic reaction conditions (pH 1) in the aqueous phase led to slow hydrolysis at the reducing[9,10] end (Scheme 3).

In contrast the reaction of DMDO with the tetrabenzylated compound **8** gave only a complex mixture of mono debenzylated heptasaccharides with no apparent selectivity.

Compound **9** was further deprotected by global deacylation with ethylene diamine followed by a selective *N*-acetylation. The free heptasaccharide azide **10** was purified by solid phase extraction followed by gel filtration. Thus traces of remaining benzylated intermediates were removed efficiently. Compound **10** was obtained in 73% yield and represents a suitable starting material for the convergent synthesis of glycopeptides[25] as well as click couplings.

The selective oxidative debenzylation of protected mono- and oligosaccharides can be carried out in high conversion using $NaBrO_3/Na_2S_2O_4$ in a biphasic water/ethyl acetate system. Under these conditions protecting groups of the ester and amide type as well as azides remained intact. The robust protocol appears to be unaffected by trace impurities causing deactivation of hydrogenation catalysts. Oxidation of the liberated hydroxyl groups was not found under the biphasic conditions.

We are grateful for the support by the Deutsche Forschungsgemeinschaft, the Fonds der Deutschen Chemischen Industrie and the European Union. Mathäus Niemietz acknowledges support by the Bavaria California Technology Center (BaCaTeC) and the Elite Network of Bavaria.

Notes and references

1 H. S. G. Beckmann and V. Wittmann, in *Org. Azides: Syntheses and Applications*, ed. S. Bräse and K. Banert, John Wiley & Sons, Chichester, 2010, pp. 469–490.
2 D. P. Gamblin, E. M. Scanlan and B. G. Davis, *Chem. Rev.*, 2009, **109**, 131–163.
3 (*a*) C. W. Tornoe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064; (*b*) W. G. Lewis, L. G. Green, F. Grynszpan, Z. Radic, P. R. Carlier, P. Taylor, M. G. Finn and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2002, **41**, 1053–1057; (*c*) W. Bröder and H. Kunz, *Carbohydr. Res.*, 1993, **249**, 221–241.
4 Y. He, R. J. Hinklin, J. Chang and L. L. Kiessling, *Org. Lett.*, 2004, **6**, 4479–4482.
5 F. Fazio and C.-H. Wong, *Tetrahedron Lett.*, 2003, **44**, 9083–9085.
6 H. Herzner, T. Reipen, M. Schultz and H. Kunz, *Chem. Rev.*, 2000, **100**, 4495–4538.
7 (*a*) F. Micheel and A. Klemer, *Adv. Carbohydr. Chem. Biochem.*, 1961, **16**, 85–103; (*b*) Z. Gyorgydeak, L. Szilagyi and H. Paulsen, *J. Carbohydr. Chem.*, 1993, **12**, 139–163.
8 (*a*) T. Tanaka, H. Nagai, M. Noguchi, A. Kobayashi and S. Shoda, *Chem. Commun.*, 2009, 3378–3379; (*b*) S. G. Gouin and J. Kovensky, *Tetrahedron Lett.*, 2007, **48**, 2875–2879; (*c*) M.-L. Larabi, C. Frechou and G. Demailly, *Tetrahedron Lett.*, 1994, **35**, 2175–2178.
9 A. V. Gudmundsdottir and M. Nitz, *Org. Lett.*, 2008, **10**, 3461–3463.
10 A. Vasella, C. Witzig, J. L. Chiara and M. Martin-Lomas, *Helv. Chim. Acta*, 1991, **74**, 2073–2077.
11 H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 155–173.
12 P. G. M. Wuts and T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, Wiley-Interscience, 2006.
13 (*a*) C. Unverzagt, G. Gundel, S. Eller, R. Schuberth, J. Seifert, H. Weiss, M. Niemietz, M. Pischl and C. Raps, *Chem.–Eur. J.*,

2009, **15**, 12292–12302; (*b*) A. Makino, K. Kurosaki, M. Ohmae and S. Kobayashi, *Biomacromolecules*, 2006, **7**, 950–957.
14 B. A. Marples, J. P. Muxworthy and K. H. Baggaley, *Synlett*, 1992, 646; R. Csuk and P. Dorr, *Tetrahedron*, 1994, **50**, 9983–9988.
15 W. Adam, J. Bialas and L. Hadjiarapoglou, *Chem. Ber*., 1991, **124**, 2377.
16 R. Rodebaugh, J. S. Debenham and B. Fraser-Reid, *Tetrahedron Lett*., 1996, **37**, 5477–5478.
17 D. Kikuchi, S. Sakaguchi and Y. Ishii, *J. Org. Chem*., 1998, **63**, 6023–6026.
18 (*a*) M. Adinolfi, G. Barone, L. Guariniello and A. Iadonisi, *Tetrahedron Lett*., 1999, **40**, 8439–8441; (*b*) M. Adinolfi, L. Guariniello, A. Iadonisi and L. Mangoni, *Synlett*, 2000, 1277–1278; (*c*) Y. Du, M. Zhang and F. Kong, *Org. Lett*., 2000, **2**, 3797–3800; (*d*) M. Adinolfi, G. Barone, A. Iadonisi and M. Schiattarella, *Tetrahedron Lett*., 2001, **42**, 5971–5972.
19 S. Sakaguchi, D. Kikuchi and Y. Ishii, *Bull. Chem. Soc. Jpn*., 1997, **70**, 2561–2566.
20 C. Unverzagt and H. Kunz, *J. Prakt. Chem*., 1992, **334**, 570–578.
21 E. Cabianca, A. Tatibouet and P. Rollin, *Pol. J. Chem*., 2005, **79**, 317–322.
22 C. Unverzagt, *Chem.–Eur. J*., 2003, **9**, 1369–1376.
23 A. Dan, M. Lergenmuller, M. Amano, Y. Nakahara, T. Ogawa and Y. Ito, *Chem.–Eur. J*., 1998, **4**, 2182–2190.
24 L. Szilagyi and Z. Gyorgydeak, *Carbohydr. Res*., 1985, **143**, 21–41.
25 C. Unverzagt, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 2350–2353.
26 C. Unverzagt, S. Eller, S. Mezzato and R. Schuberth, *Chem.–Eur. J*., 2008, **14**, 1304–1311.