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Regioselective de-*O*-benzylation of monosaccharides

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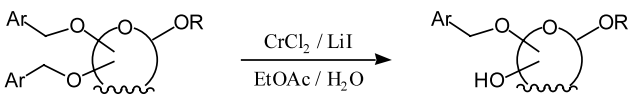
Abstract—Poly-*O*-benzylated sugars are regioselectively debenzylated using $CrCl_2$/LiI in moist EtOAc. A predictive, three-point coordination model is proposed.

Benzyl ethers are widely utilized as alcohol protecting groups.[1] They are easily installed, stable to a wide range of reagents, and readily removed in the presence of many common functionalities via catalytic hydrogenolysis, dissolving metals or Lewis/Brönsted acids. However, in the context of labile or polybenzylated compounds, e.g. carbohydrates,[2] the traditional de-*O*-benzylation conditions show poor regioselectivity and/or are too harsh.[3] A variety of elaborated benzyl ether protecting groups has been introduced to address these limitations, but they lack the robustness of unsubstituted benzyl ethers and often introduce an additional level of complexity.[1,4] In continuation of our studies of $CrCl_2$/LiI,[5] we report herein the utility of this reagent combination for the regioselective deprotection of polybenzylated carbohydrates (Eq. (1)) and propose a three-point coordination[3b,c] of the carbohydrate with Cr(II) or Cr(III) for optimal selectivity.



(1)

The scope and regioselectivity of the de-*O*-benzylation were evaluated using a panel of representative polybenzylated monosaccharides and the results are compiled in Table 1. Treatment of 3,5,6-tri-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[6] (**1**) with $CrCl_2$ and LiI at 75°C gave **2**[3b] as the sole product in good yield (entry 1). This remarkable selectivity can be explained by prior complexation[3b,c] of Cr with the oxygens of the ring and the C(5) and C(6) side chain substituents (Fig. 1). S_N2 attack at the C(5)-benzyl by iodide along pathway 'a' is comparatively unhindered and leads to the observed differential product **2**. Displacement at the C(6)-benzyl via trajectory 'b' is more sterically congested since it traverses the top face of the ring. While alternative three-point complexes are possible, e.g. between the C(3)-, C(5)-, and C(6)-oxygens, they appear less likely. This is evident in the reactivity of C(3)-acetyl derivative **3**[7] (entry 2) and allose **5**[8] (entry 3), the C(3)-epimer of **1**, both of which lose their C(5)-protecting group resulting in **4** and **6**,[9] respectively.

The strict regioselectivity observed above can be overcome in some cases by intramolecular chelation; thus, alcohol **8** is smoothly generated from **7** (entry 4) via specific rupture of the 2,6-dimethoxybenzyl (DOB) ether. When there is more than one possibility for intramolecular chelation, the more accessible ether is favored. For example, **9** gave rise to **10** (entry 5) at room temperature. Inspection of 2,4,6-tri-*O*-benzyl-*myo*-inositol orthoformate[10] (**11**) reveals only the side encompassing the C(1)-, C(2)-, and C(3)-oxygens can simultaneously coordinate to chromium and, in accordance with the predictive model, only the C(2)-benzyl ether is cleaved providing alcohol **12**[10] in good yield (entry 6). For 1,6-anhydro-α-D-glucopyranose **13**,[11] only the α-face (encompassing the ring, C(2)-, and C(4)-oxygens) can form a three-point chelate. In this case, exposure to 1 equivalent of $CrCl_2$ trimmed just the C(4)-benzyl ether to give **14**,[12] whereas 4 equivalents of $CrCl_2$ led to diol **15**[12] in excellent overall yield (entry 7).

Keywords: chromium; protecting groups; cleavage reactions; deblocking; carbohydrates.

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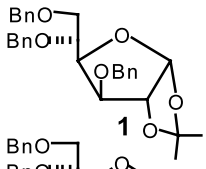
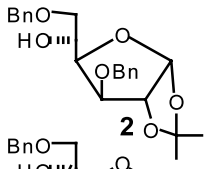
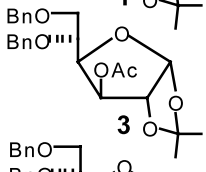
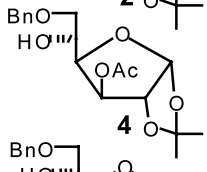
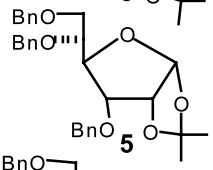
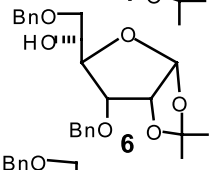
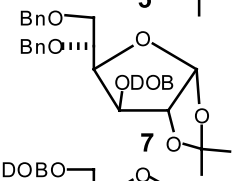
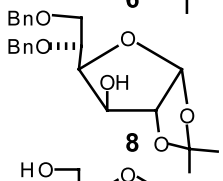
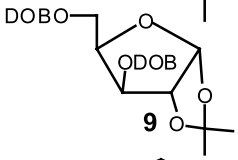
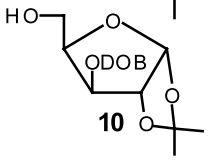
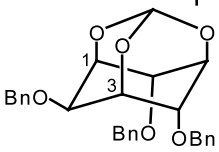
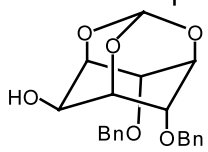
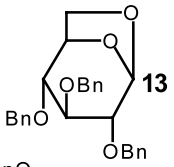
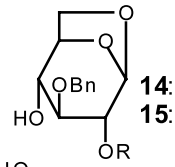
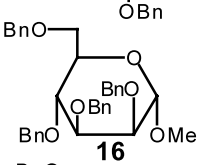
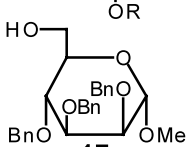
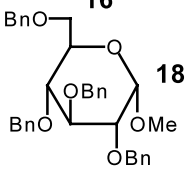
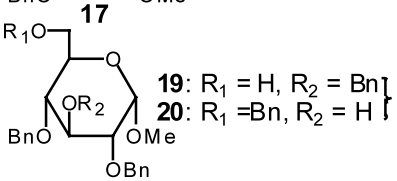
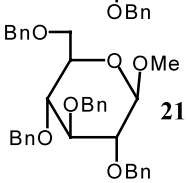
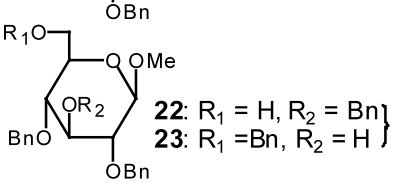
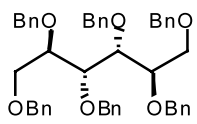
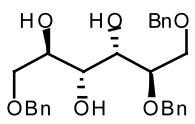
Table 1. Regioselective de-*O*-benzylation using $CrCl_2$/Li

Entry	Reactant	Product	Time (h)	Yield (%)
1	 **1**	 **2**	12	83
2	 **3**	 **4**	14	79
3	 **5**	 **6**	11	81
4	 **7**	 **8**	12[a]	82
5	 **9**	 **10**	12[b]	80
6	 **11**	 **12**	12	81
7	 **13**	 **14**: R = Bn **15**: R = H	8[c] 10	88 95
8	 **16**	 **17**	8	79
9	 **18**	 **19**: R_1 = H, R_2 = Bn **20**: R_1 =Bn, R_2 = H	12	80
10	 **21**	 **22**: R_1 = H, R_2 = Bn **23**: R_1 =Bn, R_2 = H	8	70
11	 **24**	 **25**	12	83

[a]55°C. [b]RT. [c]1 equiv $CrCl_2$, 60°C. DOB = 2,6-Dimethoxy- or Di-o-methoxybenzyl

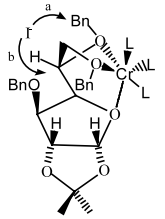


Figure 1. Chromium complex with **1**.

Application of the standard deprotection conditions to methyl 2,3,4,5-tetra-*O*-benzyl-α-D-mannopyranoside[13] (**16**) afforded **17**[14] exclusively (entry 8). On the other hand, methyl glucopyranosides are not able to adopt a stable three-point complex without energetically unfavorable conformational changes and, consequently, showed only modest regioselectivity: α-anomer **18**[15] furnished alcohols **19**[16]/**20**[17] in a 60:40 ratio (entry 9) and β-anomer **21**[15] yielded **22**/**23**[18] as a 70:30 mixture (entry 10).

Acyclic monosaccharides, with their greater conformational mobility, were generally quite reactive and undergo multiple rounds of ether cleavage. The evolution of 1,2,6-tri-*O*-benzyl-D-mannitol (**25**),[3b] a HIV aspartyl protease inhibitor,[19] directly from **24** (entry 11) is typical.

General procedure: A mixture of $CrCl_2$ (0.8 mmol; Strem Chem.) or $CrCl_3$ (1.6 mmol) and LiI (2 mmol; Aldrich Chem.) in ethyl acetate (8 mL) was heated under argon at 70°C until a brown, homogeneous solution was obtained (~0.5 h). The carbohydrate (0.2 mmol) in moist ethyl acetate (EtOAc:H_2O = 1:0.005, 1 mL) was added to the mixture at room temperature, then heated at 55–75°C for 8–14 h. The reaction was cooled to rt, quenched with water, and extracted with EtOAc. The combined organic extracts were washed with saturated aq. sodium sulfite, water, brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by silica gel chromatography afforded the respective products.

In summary, we describe an efficient, operationally simple protocol for the regioselective cleavage of benzyl ethers using $CrCl_2$/LiI under conditions suitable for polyfunctional or labile molecules. Optimal regioselectivity required three-point coordination between the carbohydrate and Cr.

Acknowledgements

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References

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd Ed.; John Wiley & Sons: New York, 1999; Chapter 2.
2. Zeigler, T. *Carbohydr. Chem.* **1998**, 21–45.
3. For examples of differential cleavage of benzyl ethers, see: (a) Madsen, J.; Viuf, C.; Bols, M. *Chem. Eur. J.* **2000**, *6*, 1140–1146; (b) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346–1353; (c) Kartha, K. P. R.; Kiso, M.; Hasegawa, A.; Jennings, H. J. *J. Carbohydr. Chem.* **1998**, *17*, 811–817; (d) Klemer, A.; Beiber, M.; Wilbers, H. *Justus Leibigs Ann. Chem.* **1983**, 1416–1421; (e) BeMiller, J. N.; Muenchow, H. L. *Carbohydr. Res.* **1973**, *28*, 253–262; (f) Angibeaud, P.; Defaye, J.; Gadelle, A.; Utille, J. P. *Synthesis* **1985**, 1123–1125; (g) Bieg, T.; Szeja, W. *Carbohydr. Res.* **1990**, *205*, C10–C11.
4. Recent examples include methoxy-substituted benzyl ethers: Yu, W.; Su, M.; Gao, X.; Yang, Z.; Jin, Z. *Tetrahedron Lett.* **2000**, *41*, 4015–4017. Halobenzyl ethers: Plante, O. J.; Buchwald, S. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148–7149. α,α-Dimethylfluorobenzyl ethers: Cho, H.-S.; Yu, J.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 8354–8355.
5. Falck, J. R.; Barma, D. K.; Baati, R.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1281–1283.
6. Ding, X.; Kong, F. *Carbohydr. Res.* **1996**, *286*, 161–166.
7. Spectral data for **3**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 3H), 1.49 (s, 3H), 1.91 (s, 3H), 3.68 (dd, 1H, J = 5.4, 10.2 Hz), 3.84–3.96 (m, 2H), 4.36 (dd, 1H, J = 3.0, 9.0 Hz), 4.47 (dd, 2H, J = 3.9, 7.8 Hz), 4.60 (s, 2H), 4.78 (d, 1H, J = 11.4 Hz), 5.31 (d, 1H, J = 2.7 Hz), 5.86 (d, 1H, J = 3.6 Hz), 7.20–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.91, 26.40, 26.74, 71.04, 72.62, 73.61, 74.98, 76.22, 77.62, 83.17, 104.91, 112.33, 127.69, 127.76, 127.86, 128.04, 128.48, 128.54, 138.21, 138.45, 169.73. **4**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H), 1.51 (s, 3H), 2.10 (s, 3H), 2.69 (d, 1H, J = 5.2 Hz), 3.61 (dd, 1H, J = 6.4, 9.6 Hz), 3.77 (dd, 1H, J = 2.4, 9.6 Hz), 3.82–3.94 (m, 1H), 4.23 (dd, 1H, J = 2.4, 8.8 Hz), 4.53 (d, 1H, J = 3.6 Hz), 4.55–4.63 (m, 2H), 5.32 (d, 1H, J = 2.8 Hz), 5.89 (d, 1H, J = 4.0 Hz), 7.20–7.40 (m, 5H). **7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 3H), 1.52 (s, 3H), 3.78 (s, 6H), 3.62–3.71 (m, 1H), 4.03–4.07 (m, 1H), 4.18 (d, 1H, J = 2.8 Hz), 4.24 (dd, 1H, J = 2.8, 9.2 Hz), 4.57–4.62 (m, 3H), 4.72–4.80 (m, 4H), 5.89 (d, 1H, J = 3.6 Hz), 6.52 (d, 2H, J = 8.0 Hz), 7.22–7.35 (m, 11H). **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 3H), 1.46 (s, 3H), 3.68–3.73 (m, 2H), 3.77 (s, 6H), 3.80 (s, 6H), 4.04 (dd, 1H, J = 3.3 Hz), 4.34–4.39 (m, 1H), 4.59–4.61 (m, 1H), 4.65–4.71 (m, 4H), 5.87 (d, 1H, J = 3.9 Hz), 6.53 (dd, 4H, J = 1.8, 8.1 Hz), 7.19–7.26 (m, 2H). **10**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3H), 1.49 (s, 3H), 2.90 (t, 1H, J = 6.8 Hz), 3.78–3.81 (m, 2H), 3.84 (s, 6H), 4.05 (d, 1H, J = 3.6 Hz), 4.27–4.29 (m, 1H), 4.59 (d, 1H, J = 10 Hz), 4.71 (d, 1H, J = 4.0 Hz), 4.84 (d, 1H, J = 10.4 Hz), 5.97 (d, 1H, J = 4.0 Hz), 6.57 (d, 2H, J = 8.4 Hz), 7.25–7.29 (m, 1H).
8. Koell, P.; Lendering, U. *J. Carbohydr. Chem.* **1987**, *6*, 281–293.
9. Stepowska, H.; Zamojski, A. *Tetrahedron* **1999**, *55*, 5519–5538.
10. Billington, D. C.; Baker, R.; Kulagowski, J. J.; Mawer, I. M.; Vacca, J. P.; Jane deSolms, S.; Huff, J. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1423–1429.

11. Micheel, F.; Brodde, O. E.; Reinking, K. *Justus Leibigs Ann. Chem.* **1974**, 124–136.
12. Carmen, C. M.; Martin-Lomas, M. *Carbohydr. Res.* **1988**, *175*, 193–199.
13. Fuegedi, P.; Liptak, A.; Nanasi, P.; Neszmelyi, A. *Carbohydr. Res.* **1982**, *107*, C5–C9.
14. Chervenak, M. C.; Toone, E. J. *Bioorg. Med. Chem.* **1996**, *4*, 1963–1978.
15. Briner, K.; Vasella, A. *Helv. Chim. Acta* **1992**, *75*, 621–637.
16. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990–2016.
17. Chiu-Machado, I.; Castro-Palomino, J. C.; Madrazo-Alonzo, O.; Lopetegui-Palacios, C.; Verez-Bencomo, V. *J. Carbohydr. Chem.* **1995**, *14*, 551–562.
18. Kanaoka, M.; Yano, S.; Kato, H.; Nakada, T. *Chem. Pharm. Bull.* **1986**, *34*, 4978–4983.
19. Sauve, G.; Bouzide, A. *PCT Int. Appl.* 2000, 152 pp, WO 0066524.