Chinese Chemical Letters Vol. 11, No. 11, pp. 941–944, 2000

Selective De-O-acetylation in TCP-containing Carbohydrate Structures with Magnesium Methoxide

Zhi Hui QIN, Hui LI, Meng Shen CAI, Zhong Jun LI*

Department of Bioorganic Chemistry, School of Pharmaceutical Sciences, Beijing Medical University, Beijing 100083

Abstract: Magnesium methoxide can be used for TCP-containing substrates to remove acetyl group successfully while leaving the TCP- group virtually intact.

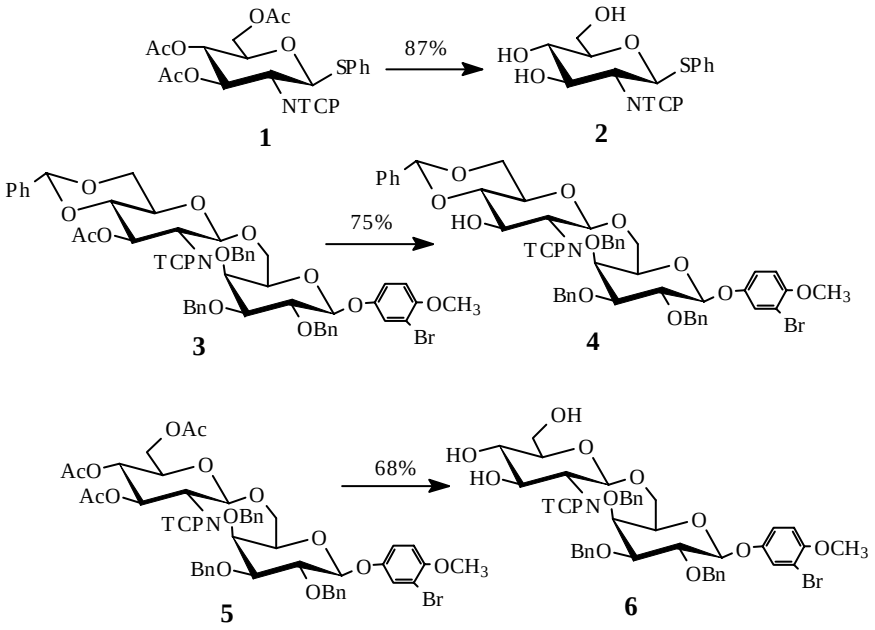
Keywords: De-O-acetylation, TCP, magnesium methoxide.

β-Glycosides of 2-acetamido-2-deoxy-sugars are widespread in naturally occurring glycoproteins, glycolipids and other glycoconjugates[1]. Synthetic efforts in the construction of these biologically significant type of glycosides have led to the development of a variety of methods for C-2 nitrogen protection, such as phthaloyl(phth)[2], dichloro-pthaloyl(DCPth)[2], tetrachloro-phthaloyl (TCP)[4], 2,2.2-trichloroethoxycarbonyl (Teoc)[5] functionalities *etc*. Of all these protection groups, TCP has received more attention in recent years due to its strong 1,2-trans directing nature and ease of removal[6].

But, due to its manifested base liability, how to selectively remove acetyl group in a TCP-containing carbohydrate structure has become an important problem in oligosaccharide synthesis. To solve this problem, acid-catalyzed de-O-acetylation using HCl in aqueous organic solvent has been used by Debenbam *et al*[7] for a N-TCP protected glucosamine moiety, but this approach may be unsuitable for carbohydrate structures containing acid-sensitive glycosyl bonds (such as *p*-methoxyphenol glycoside[8]) or other acid liable protecting groups. Indeed, methanolic sodium methoxide (NaOMe/MeOH) has also been utilized for de-O-acetylation in presence of TCP group[8,9], however, the reaction conditions, such as time, temperature, and concentration of the base must be strictly controlled.

Magnesium methoxide is another de-O-acetylation reagents which can differentiate acetyl and benzoyl groups during the deprotection step[10]. To our delight, we have discovered that it can be used for TCP-containing substrates to remove acetyl group successfully while leaving the N-TCP group virtually intact. In our experiment, one monosaccharide (compound **1**, phenyl 3,4,6-tri-O-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranothioglycoside) and two disaccharide [compound **3**, 1-O-(3-bromo-4-methoxy)phenyl-(3-O-acetyl-4,6-O-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-galactopyranoside), compound **5**, 1-O-(3-bromo-4-methoxy)phenyl-(3,4,6-tri-O-acetyl-2-deoxy-2-tetrachlorophthalimido-

β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-galactopyranoside] containing one and three acetyl group respectively were chosen to act as substrates to show the effectiveness of our approach (structures and yields were outlined as follows).



Reaction condition: $Mg(OMe)_2$/THF-MeOH(3:1), 0-5°C.

In the experiment, magnesium methoxide was prepared according to Wiley's method[11], after drying, it was placed in a well stoppered bottle and can be used within 2-3 months. Appropriate amount of magnesium methoxide was added to the solution of substrate (1 equiv per OAc) directly. As showed above, under such conditions, acetyl groups were removed effectively, while other protecting groups, such as TCP group, 4,6-O-benzylidene group and 3-bromo-4-methoxyl phenyl glycoside *etc*. were intact.

In order that TCP protection can be accepted as a general tool in oligosaccharide synthesis, compatibility with certain deacetylation conditions should be of particular significance. Our experiments have showed that magnesium methoxide has remarkable compatibility with the N-TCP protecting group.

The general procedure for selective de-O-acetylation is as follows: Freshly pre-pared magnesium methoxide (1equiv per OAc) was added to a solution of compound (**1**-**3**) in THF-MeOH (3:1) (1equiv, 0.1M soln.). The mixture was stirred at 0-5°C in an ice-bath or standed in refrigerator for several hours, depending on the scale of the reaction. After completion of the reaction, the mixture was neutralized with acetic acid, concen- trated and purified by column chromatography.

Acknowledgments

The project was supported by the National Natural Sciences Foundation of China and a grant from the Ministry of Science and Technology of P. R. China.

Reference and notes

1. J. Banoub, P. Boullanger, D. Lafont, *Chem. Rev.*, **1992**, 1165.
2. R. U. Lemeiux, R. M. Ratcliffe, *Can. J. Chem*., **1979**, *57*, 1244.
3. M. Lergenmuller, Y. Ito and T. Ogawa, *Tetrahedron*, **1988**, *54*, 1381.
4. **a**. J. S. Debenham, R. Madson, C. Robert, B. Fraser-Reid, *J. Am. Chem. Soc*., **1995**, *117*, 3302.
   b. J. C. Castro-Palomino, R. R. Schmidt, *Tetrahedron Lett*., **1995**, *36*, 5343.
5. U. Ellervik, G. Magnusson, *Carbohydr. Res.*, **1996**, *28*, 251.
6. J. S. Debenham, R.Madsen, C. Roberts, B. Fraser-Reid, *Liebigs Ann*., **1997**, 791.
7. J. S. Debenham, R. Rodebaugh, B. Fraser-Reid, *J. Org. Chem.*, **1997**, *62*, 4591.
8. U. Ellervik and G. Magnusson, *J. Org. Chem.*, **1998**, *63*, 314.
9. L. G. Lay, L. Manzoni, R. R. Schmidt, *Carbohydr. Res*., **1998**, *310*, 157
10. S. Nilsson, H. Lonn, T. Norberg, *J. Carbohydr. Chem*., **1991**, *10*, 1023.
11. L. I. Smith, P. F. Wiley, *J. Am. Chem. Soc*., **1946**, *68*, 887.
12. Selected physical data of compound **2**, **4**, **6**.

Phenyl 2-deoxyl-2-tetrachlorophthlimido-β-D-glucopyranothioglycoside (2):

Crude product was purified by column chromatography, eluting with 20:1$CHCl_3$/ MeOH to afford the title compound in 87% yield. Rf: 0.22 ($CHCl_3$/MeOH 20:1). $[\alpha]_D$ 72.1(*c* 1.22, DMF). ^{1}H-NMR(400 MHz, DMSO-d_6): 7.20-7.37 (m, 5H, ArH), 5.58 (d, 1H, J=4.62 Hz, OH), 5.50 (d, 1H, J=10.38 Hz, H-1), 5.36 (d, 1H, J=4.52 Hz, OH), 4.73 (br, 1H, OH), 4.02-4.08 (m, 1H, H-3′), 3.90-3.95 (m, 1H, H-2′), 3.76-3.79 (m, 1H, H-6a), 3.54-3.57 (m, 1H, H-6b), 3.39-3.43(m, 1H, H-4), 3.18-3.31 (m, 1H, H-5). ^{13}C-NMR (100 MHz, DMSO-d_6): 163.1(C=O, TCP), 162.7(C=O, TCP), 139.1, 138.9, 132.9, 130.2, 129.1, 128.7, 128.4, 127.5, 127.2, 127.1(Ar-C), 82.1(C-1), 81.8(C-5), 71.6(C-3), 70.1(C-4), 60.8(C-6), 57.3(C-2). Anal. Calcd. For $C_{20}H_{15}NO_6SCl_4$: C, 44.54; H, 2.80; N, 2.60. Found: C, 44.34; H, 2.89; N, 2.35.

1-O-(3-Bromo-4-methoxy)-phenyl-(4.6-O-benzylidene-2-deoxy-tetrachlorophthali-mido-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-β-D-galactopyranoside) (4):

The crude product was purified by column chromatography, eluting with 25:1 $CHCl_3$/MeOH to afford the title compound in 75% yield. Rf: 0.32($CHCl_3$/MeOH 20:1). $[\alpha]_D$ -36.1(*c* 1.11, $CHCl_3$). IR: 3484cm^{-1}(-OH), 1717cm^{-1}(C=O, TCP). ^{1}H-NMR(400 MHz, $CDCl_3$) (δ ppm): 7.24-7.44 (m, 20H, ArH), 7.215 (d, 1H, J_m=2.84 Hz, OMp), 6.94 (dd, 1H, J_m=2.84 Hz, J_o=8.93 Hz, OMp), 6.81 (d, 1H, J_o=9.02 Hz, OMp), 5.50 (s, 1H, PhC<u>H</u>), 5.25 (d, 1H, J=8.44 Hz, H-1′), 4.97, 4.94, 4.65, 4.62 (ABq, J=11.30 Hz, OCH_2Ph), 4.88, 4.85, 4.80, 4.78(ABq, J=10.90 Hz, OCH_2Ph), 4.67-4.74(m, 3H, H-1 and O<u>C</u>H$_2$Ph), 4.52(dd, 1H, J=8.63 Hz, 10.41 Hz, H-3′), 4.17-4.22 (m, 2H, H-2', H-6a), 3.98 (dd, 1H, J=7.83, 9.64 Hz, H-2), 3.88-3.96 (m, 1H, H-6a′), 3.82 (s, 3H, OCH_3), 3.68-3.80(m, 3H, H-4, H-4′, H-6b′), 3.49-3.55 (m, 4H, H-3, H-5, H-6b, H-5′), 2.03(br, 1H, -OH). ^{13}C-NMR (100 MHz, $CDCl_3$): 151.8, 151.5(C1, C4, OMp), 140.4(Ar-C, TCP), 138.5, 138.3, 138.2, 136.7, 129.4, 128.42, 128.4, 128.3, 128.2, 128.2, 127.9, 127.7, 127.6, 127.5, 127.0, 126.2(Ar-C), 122.9, 117.4, 112.5, 111.5(C2, C3, C5, C6, OMp), 103.0(C-1), 101.9 (Ph<u>C</u>H), 98.2(C-1′), 81.9(C-3), 81.9(C-4′), 78.8(C-2), 75.4(OCH_2Ph), 74.6(OCH_2Ph), 73.4(C-5), 73.3(C-4), 73.0(OCH_2Ph), 68.4 (C-6), 68.3 (C-6′), 67.8(C-3′), 66.1(C-5′), 57.0(C-2′), 56.66(OCH_3). MALDI-TOF: 1176.1$(M+Na)^+$, 1191.9 $(M+K)^+$. Anal. Calcd. for $C_{55}H_{48}O_{13}NCl_4Br$: C, 57.30; H, 4.20; N, 1.22. Found: C, 56.97; H, 4.16; N, 1.07.

3-Bromo-4-methoxyphenyl (2-deoxy-2-tetrachlorophthalimido-B-D-glucopyranosyl) -(1-6)-(2, 3, 4-tri-O-benzyl-β-D-galatopyranoside) (6)

The crude product was purified by column chromatography, eluting with 1:4

EtOAc/cyclohexane to afford the title compound in 68% yield. $[\alpha]_D$ -32.9 (*c* 0.73, $CHCl_3$). Rf: 0.30 (EtOAc/Cyclohexane 1:4). ^{1}H-NMR(400 MHz, $CDCl_3$): 7.22-7.30 (m, 15H, ArH), 7.18(d, 1H, J_m=2.85Hz, ArH, OMp), 6.89(dd, 1H, J_o=8.94 Hz, J_m=2.87 Hz, ArH, OMp), 6.74(d, 1H, J_o=9.06 Hz, ArH, OMp), 5.20(d, 1H, J=8.3Hz, H-1′), 4.92, 4.89, 4.62, 4.59(ABq, J=11.5Hz, OCH_2Ph), 4.85, 4.82, 4.78, 4.75(ABq, 11.1Hz, OCH_2Ph), 4.70, 4.67, 4.64, 4.61(ABq, J=11.7Hz, OCH_2Ph), 4.74(d, J=8.0Hz, H-1), 4.14-4.19(m, 1H, H-3′), 4.01-4.06(m, 1H, H-2′), 3.96(dd, 1H, J=9.6Hz, 7.9Hz, H-2), 3.83-3.87(m, 1H, H-5), 3.80(s, 3H, OCH_3), 3.69-3.77 (m, 4H, H-4, H-6a, H-6a′, H-6b′), 3.64(t, 1H, J=9.08Hz, H-4′), 3.46-3.53(m, 2H, H-3, H-6b), 3.29-3.32(m, 1H, H-5′). ^{13}C-NMR(100 MHz, $CDCl_3$): 163.6(C=O, TCP), 151.7, 151.3(C1, C4, OMp), 140.2(Ar-C, TCP), 138.4, 138.3, 138.2, 129.7, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.4, 127.1(Ar-C), 122.8, 117.2, 112.5, 111.5(C2, C3, C5, C6, OMp), 102.8(C-1), 97.8(C-1′), 81.95(C-3), 78.7(C-2), 75.4(C-5′), 75.3 (OCH_2Ph), 74.5(OCH_2Ph), 73.4(C-6), 73.0(OCH_2Ph), 71.3(2C, C-3′, C-4′), 67.8 (2C, C-5, C-4), 61.6(C-6′), 57.1(C-2′), 56.7($O\underline{C}H_3$). Anal. Calcd. for $C_{48}H_{44}O_{13}NCl_4Br.1/2H_2O$: C, 53.71; H, 4.10; N, 1.30. Found: C, 53.57; H, 4.17; N, 1.30.

Received 13 April 2000