One-pot transformation of glycopyranosylcyanides to N-(t-butoxycarbonyl)methylamines

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Abstract—Protected glycopyranosylcyanides were transformed into the corresponding N-tert-butoxycarbonyl-glycopyranosyl methylamines in a one-pot transformation in high yields. This general method is applicable to glycopyranosylcyanides bearing common O- and N-protecting groups frequently used in carbohydrate chemistry. © 2001 Published by Elsevier Science Ltd.

The synthesis of C-glycosides as stable mimetics of natural carbohydrate linkages has attracted strong interest in the last few decades and numerous methods for their synthesis have been published.[1] Natural O- and N-glycosidic linkages in glycoproteins and glycopeptides are susceptible to chemical hydrolysis and hydrolase activity. Their C-glycoside analogues are therefore useful tools in the field of glycobiology.[2]

The aim of our current research is the synthesis of C-glycopeptides as inhibitors of glycoamidases. There are two general approaches to the synthesis of C-glycosidic analogues of O- and N-linked glycopeptides.[3] The most common is the incorporation of C-glycosyl amino acids into a peptide chain.[4] In the synthesis of N-glycoside mimics, an alternative is the coupling of a glycosylmethylamine with the side-chain of an aspartic acid residue in a pre-assembled peptide.[5] We chose the latter strategy.

Wang et al. reported the synthesis of a high-mannose C-glycopeptide as a potential inhibitor of glycoamidases.[5] The hydrogenation of the glucopyranosyl-cyanide 1 and temporary Boc-protection of the resulting primary amine in a separate step (Scheme 1) represents a crucial transformation in their synthesis. In our hands the reduction of 1 did not yield the corresponding amine, but instead the aldimine 3 (Scheme 2), as shown by a characteristic doublet at 7.51 ppm ($J = 4$ Hz) in the ^{1}H NMR for the imine proton. The formation of 3 occurs via the addition of the desired primary amine to the intermediate imine followed by loss of ammonia.[6]

To circumvent this problem we developed a one-step procedure based on the work of Saito et al. who reported the one-pot transformation of various 2-azido alcohols into 2-N-Boc-amino alcohols.[7] The trapping of the amine as a Boc-carbamate prevents the formation of the aldimine. The transformation proceeds under mild conditions with short reaction times and gives good yields. The results are summarised in Table 1.
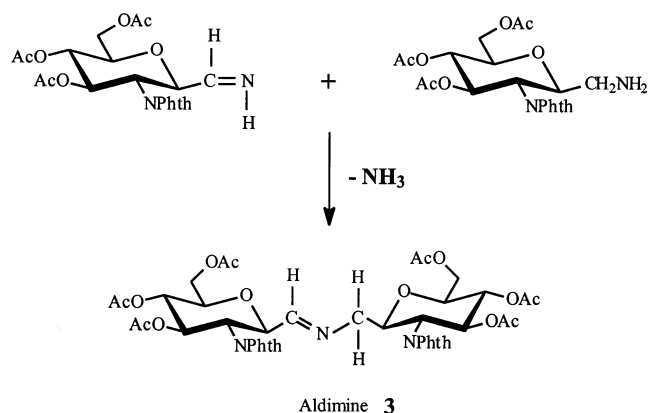
The results show that our procedure is compatible with acetate and benzoate ester protecting groups, which are
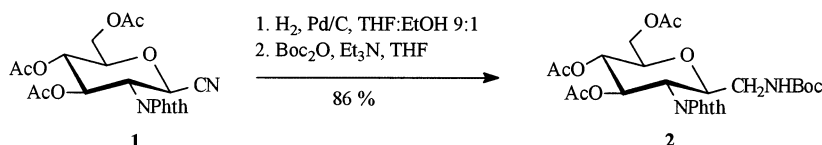
Scheme 1. Hydrogenation of a glucopyranosylcyanide followed by Boc-protection in a two-step procedure published by Wang et al.[5] (Phth: Phthalimido).

Scheme 2. Formation of the aldimine using the conditions of Wang et al.[5]

frequently used in carbohydrate chemistry. Moreover, the procedure can be applied to *N*-phthalimido protected 2-amino-2-deoxy-sugars and thus offers quick and easy access to precursors for the synthesis of *C*-glycosidic analogues of *N*-linked glycopeptides.

Interestingly, the yield for the transformation of the glucopyranosylcyanide **1** is poor (52%) when the reaction is performed under neutral conditions. The addition of triethylamine increases the yield to 97%. Saito et al. preferred neutral conditions for the reduction/protection of azides to prevent side reactions caused by the base.[7]

This paper establishes a straightforward method for the synthesis of glycopyranosylmethylamines. The Boc group can then be cleaved quantitatively by standard procedures.[8]

Experimental

The standard procedure is given in Table 1.

***N*-*tert*-Butoxycarbonyl-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)methylamine**:
Glucopyranosylcyanide **1** (100 mg, 0.23 mmol) was processed using the standard procedure. After flash chromatography on silica using PE:EA (1:1) as the eluent, 120 mg (97%) of the product were obtained as a white foam. ^{1}H NMR (300 MHz, CDCl$_3$): δ ppm: 7.83–7.71 (m, 4H, phthaloyl), 5.80 (t, 1H, $J=9$ Hz,

Table 1. One-pot transformation of glycopyranosylcyanides to the corresponding Boc-carbamates

R-CN ⟶ R-CH$_2$NHBoc	
Glycopyranosylcyanide	**Yield %** RCH$_2$NHBoc
1	**97**[‡]
4	**73**
5	**83**
6	**51**

[¶]**All reactions conducted under the following standard conditions:** Triethylamine (10 eq), di-*tert*-butyl-dicarbonate (3 eq) and 10 % Pd/C (0.5 g/g of substrate) were added sequentially to a solution of the glycopyranosylcyanide in EtOH/THF (5:3) and the mixture stirred for 6 h under a hydrogen atmosphere at 30 °C. After completion the reaction mixture is filtered and the solvent evaporated. The residue is taken up in CH$_2$Cl$_2$, the organic phase washed with sat. NaHCO$_3$, brine and water, dried over Na$_2$SO$_4$ and chromatographed.
[‡]When working under neutral conditions the yield is reduced to 52%.

H-3), 5.15 (t, 1H, $J=10$ Hz, H-4), 4.84 (m, 1H, NH), 4.51 (m, 1H, H-1), 4.38–4.27 (m, 2H, H-2, H-6a), 4.14 (dd, 1H, $J=12.5$ and 2.1 Hz, H-6b), 3.84 (dq, 1H, $J=10.3$ and 2 Hz, H-5), 3.33–3.30 (m, 2H, CH$_2$N), 2.12, 2.03, 1.83 (3s, 3H each, O-Ac), 1.39 (s, 9H, Boc). Anal. calcd for $C_{26}H_{32}O_{11}N_2$: C, 56.93; H, 5.88; N, 5.11. Found: C, 56.53; H, 6.18; N, 4.92.

***N*-*tert*-Butoxycarbonyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(3,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)methylamine**: Glucopyranosylcyanide **4** (1.27 g, 1.54 mmol) was processed using the standard procedure. After flash chromatography on silica using PE:EA (1:1) as the eluent, 1.04 g (73%) of the product were obtained as a white foam. ^{1}H NMR (300 MHz, CDCl$_3$): δ ppm: 7.88–7.72 (m, 8H, phthaloyl), 5.78–5.69 (m, 2H, H-3, H-3′), 5.46 (d, 1H, $J=9$ Hz, H-1′), 5.14 (t, 1H, $J=9$ Hz, H-4′), 4.69 (m, 1H, NH), 4.44–4.40 (m, 2H, H-1, H-6′a), 4.32–4.23 (m, 2H, H-2′, H-6a), 4.17 (t, 1H, $J=10$ Hz, H-2), 4.05 (dd, 1H, $J=12$ and 2 Hz, H-6′b), 3.92 (t, 1H, $J=9$ Hz, H-4), 3.80 (dq, 1H, $J=9$ and 2 Hz, H-5′), 3.70–3.63 (m, 2H, H-5, H-6b), 3.21 (m, 2H, CH$_2$N), 2.13, 1.99, 1.96, 1.87, 1.82 (5s, 3H each, O-Ac), 1.54 (s, 9H, Boc). Anal. calcd for $C_{44}H_{49}O_{19}N_3$: C, 57.20; H, 5.35; N, 4.55. Found: C, 56.81; H, 5.52; N, 4.46.

***N*-*tert*-Butoxycarbonyl-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)methylamine**: Galactopyranosylcyanide **5** (72 mg, 0.2 mmol) was processed using the standard procedure. After flash chromatography on silica using PE:EA (1:1) as the eluent, 77 mg (83%) of the product were obtained as a white foam. ^{1}H NMR (300 MHz, CDCl$_3$): δ ppm: 5.35 (dd, 1H, $J=3$ and 1 Hz, H-4), 5.05 (t, 1H, $J=9$ Hz, H-2), 4.96 (dd, 1H, $J=7$ and 4 Hz, H-3), 4.84 (m, 1H, NH), 4.08 (dd, 1H, $J=7$ and 5 Hz, H-6a), 3.99 (dd, 1H, $J=7$ and 5 Hz, H-6b), 3.82 (td, 1H, $J=6$ and 1 Hz, H-5), 3.48–3.38 (m, 2H, H-1, CH$_2$N), 3.18–3.07 (m, 1H, CH$_2$N), 2.09, 1.99, 1.98, 1.90 (4s, 3H each, O-Ac), 1.38 (s, 9H, Boc). Anal. calcd for $C_{20}H_{31}O_{11}N$: C, 52.06; H, 6.77; N, 3.04. ∈Found: C, 51.91; H, 6.99; N, 3.00.

***N*-*tert*-Butoxycarbonyl-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)methylamine**: Xylopyranosylcyanide **6** (180 mg, 0.38 mmol) was dissolved in EtOH alone using the conditions of the standard procedure. After flash chromatography on silica using PE:EA (2:1) as the eluent, 111 mg (51%) of the product were obtained as a colourless syrup. ^{1}H NMR (300 MHz, CDCl$_3$): δ ppm: 7.96–7.26 (m, 15H, 3×O-Bz), 5.87 (t, 1H, $J=10$ Hz, H-3), 5.42–5.34 (m, 2H, H-2, H-4), 5.02 (m, 1H, NH), 4.41 (q, 1H, $J=6$ Hz, H-5a), 3.75–3.61 (m, 2H, H-1, CH$_2$N), 3.54 (t, 1H, $J=10$ Hz, H-5b), 3.22–3.14 (m, 1H, CH$_2$N), 1.42 (s, 9H, Boc). Anal. calcd for $C_{32}H_{33}O_9N$: C, 66.77; H, 5.78; N, 2.43. Found: C, 66.82; H, 6.02; N, 2.70.

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