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# Synthesis of Glycosyl Chlorides with Acid-Labile Protecting Groups

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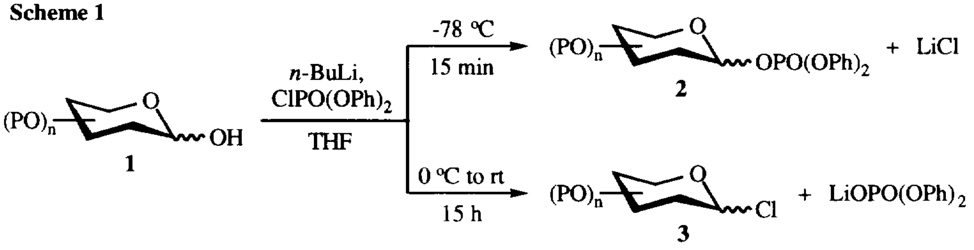
**Abstract:** Glycosyl chlorides with acid-labile protecting groups were prepared from their corresponding alcohols under basic conditions in good yields. The synthesis of a 1,6-C-linked disaccharide was carried out via reaction of a glycosyl chloride with an aldehyde in the presence of samarium(II) diiodide. Copyright © 1996 Elsevier Science Ltd

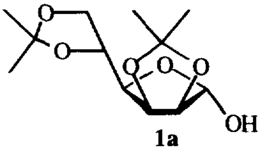
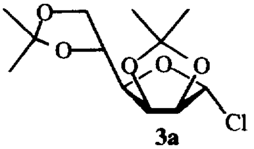
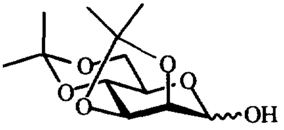
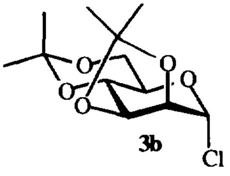
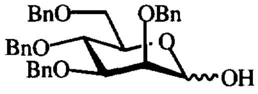
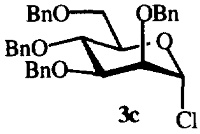
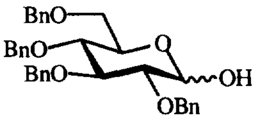
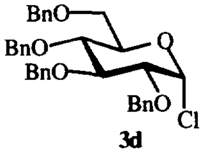
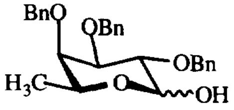
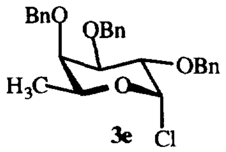
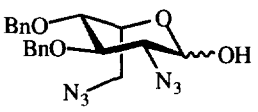
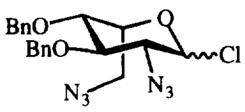
The utilities of glycosyl chlorides in the formation of glycosidic bonds have been appreciated for a long time. Anomeric carbocations,[1] radicals[2] or carbanions[3] can be generated from glycosyl chlorides easily for the study of various reactions. Normally, glycosyl chlorides are prepared under acidic conditions, and therefore the protecting groups used are often acid-stable. In certain cases, $Ph_3P/CCl_4$[4] or chloroenamine[5] has been used in the synthesis of glycosyl chlorides under neutral conditions. Here we report the synthesis of glycosyl chlorides under basic conditions (Scheme 1). This method is believed to be useful for the transformation of glycosyl chlorides under acid-sensitive conditions.

**Scheme 1**



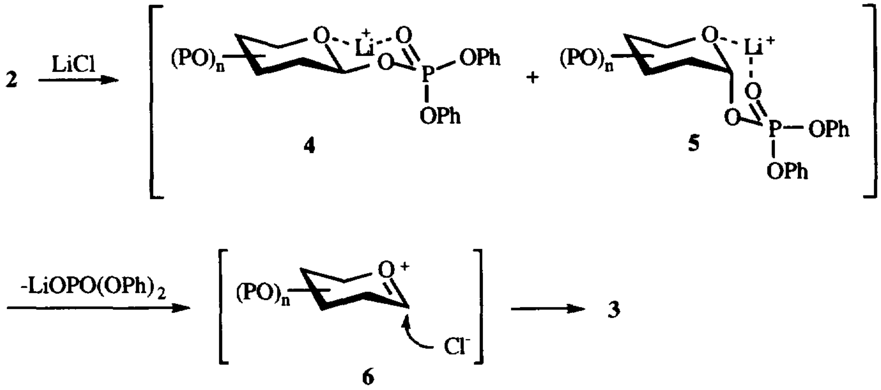
This new reaction was discovered incidentally during the synthesis of glycosyl diphenylphosphates[6], where the corresponding alcohol was usually treated with one equivalent of *n*-butyl lithium at -78 °C followed by addition of one equivalent of chlorodiphenylphosphate (Scheme 1). It was found that after the reaction was warmed up to room temperature and stirred overnight, the only isolated product was, however, glycosyl chloride. We have since optimized the condition for the synthesis of glycosyl chlorides. Typically the phosphorylation

**Table 1**: Synthesis of glycosyl chlorides from the corresponding alcohols.

| entry | glycosyl alcohol | glycosyl chloride | yield |
|---|---|---|---|
| 1 |  **1a** |  **3a** | 92% |
| 2 |  **1b** |  **3b** | 86% |
| 3 |  **1c** |  **3c** | 88% |
| 4 |  **1d** |  **3d** | 83% |
| 5 |  **1e** |  **3e** | 88% |
| 6 |  **1f** |  **3f** | 78%<br>(α/β=4/1) |

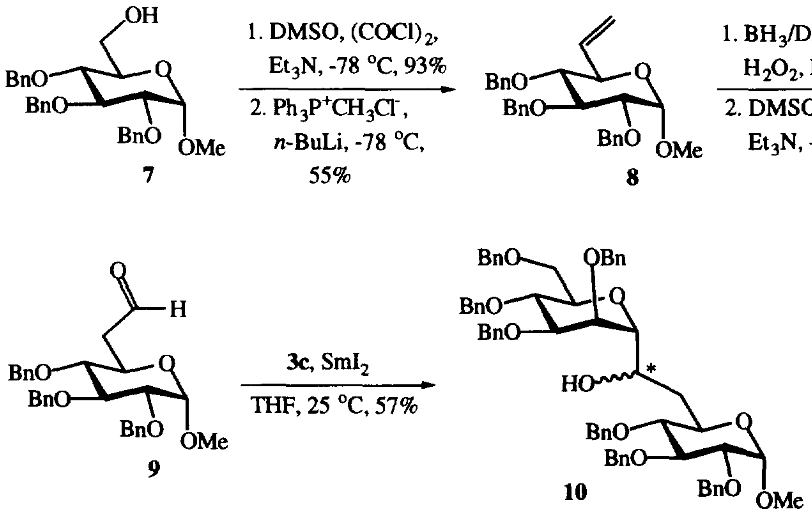
reaction was carried out at 0 °C then warmed up to 25 °C and stirred for additional 15 hours. The results are shown in Table 1.[7] In entries 1, 2, 3, 4 and 5, only α-anomers were isolated in >80% yield. In entry 6, compound **1f**[8] generated from neomycin B, was converted to **3f** in 78% yield as a 4:1 (α/β) mixture. The stereochemistry of glycosyl chlorides was determined based on the coupling constant of $H_1$.[7] While the mechanism for this new reaction is unclear, it perhaps proceeds through the complex of glycosyl diphenylphosphate **2** and lithium cation to form intermediates **4** and **5**. Due to the Lewis acid nature of $Li^+$, elimination may occur to form the oxonium ion **6** which then reacts with chloride to give α-glycosyl chloride.

**Scheme 2**



Recently, Sinay et al. have reported that glycosyl samarium (III) derivatives, generated from 2-deoxyglycosyl chlorides, undergo the Barbier type reaction with carbonyl compounds to form C-glycosides.[9] To illustrate the utility of glycosyl chlorides prepared in this study, the synthesis of a C-linked 1,6-disaccharide is indicated in Scheme 3. The aldehyde **9**, prepared from compound **7**[10] in four steps, was used as acceptor to form the 1,6-C-linked disaccharide **10** in 57% yield after purification by silica gel column chromatography.[11] Work is in progress to utilize these glycosyl chlorides in the synthesis of O- or C-glycosides.

**Scheme 3**



(the ratio of carbinols = 6:1)

## References and Notes

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7. Compounds **1a**, **1c**, **1d** and **1e** are commercially available. Compound **1b** was prepared by following the procedure of ref. 12. Compounds **3a**, **3b** and **3d** gave spectral data in agreement with the reported values.[5] Spectra data of other compounds are shown below. **1f (major/minor):** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.26 (m, 10 H, Ar-*H*), 5.14-5.07 (m, 1 H, H-1), 4.65-4.43 (m, 4 H, -O$CH_2$Ph), 3.99/4.26 (ddd, $J$ = 7.9, 5.7, 2.4/8.0, 5.5, 3.0 Hz, 1 H, H-5), 3.89/3.80 (t, $J$ = 3.4/4.4 Hz, 1 H, H-3), 4.69/3.62 (dd, $J$ = 12.6, 7.9/12.7, 7.8 Hz, 1 H, H-6), 3.61/3.49 (m, 1 H, H-2), 3.35/3.48 (m, 1 H, H-4), 3.23/3.30 (dd, $J$ = 12.6, 5.6/12.7, 5.5 Hz, 1 H, H-6). **3c:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.16 (m, 20 H), 6.10 (d, $J$ = 1.4 Hz, 1 H, H-1), 4.89 (d, $J$ = 10.7 Hz, 1 H), 4.79-4.49 (m, 7 H), 4.18 (dd, $J$ = 9.4, 3.0 Hz, 1 H), 4.09 (t, $J$ = 9.4 Hz, 1 H), 4.01 (m, 1 H), 3.87 (dd, $J$ = 3.1, 1.8 Hz, 1 H), 3.81 (dd, $J$ = 11.2, 4.4 Hz, 1 H), 3.69 (dd, $J$ = 11.2, 1.7 Hz, 1 H). **3e:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.25 (m, 15 H), 6.14 (d, $J$ = 3.8 Hz, 1 H, H-1), 4.99 (d, $J$ = 11.4 Hz, 1 H), 4.89 (d, $J$ = 11.8 Hz, 1 H), 4.79-4.71 (m, 3 H), 4.65 (d, $J$ = 11.4 Hz, 1 H), 4.21 (dd, $J$ = 9.8, 3.8 Hz, 1 H), 4.16 (q, $J$ = 6.5 Hz, 1 H), 3.98 (dd, $J$ = 9.8. 2.8 Hz, 1 H), 3.69 (d, $J$ = 2.8 Hz, 1 H), 1.16 (d, J = 6.5 Hz, 3 H). **3f ($\alpha$ isomer):** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.19 (m, 10 H), 6.00 (d, $J$ = 2.5 Hz, 1 H, H-1), 4.74 (d, $J$ = 11.5 Hz, 1 H), 4.66 (d, $J$ = 11.7 Hz, 1 H), 4.56 (d, $J$ = 11.5 Hz, 1 H), 4.44 (d, $J$ = 11.7 Hz, 1 H), 4.44-4.40 (m, 1 H) 3.85 (dd, $J$ = 4.3, 2.6 Hz, 1 H), 3.78 (t, $J$ = 3.2 Hz, 1 H), 3.63 (dd, $J$ = 12.9, 8.0 Hz, 1 H), 3.54 (t, $J$ = 3.2 Hz, 1 H), 3.22 (dd, $J$ = 12.9, 5.0 Hz, 1 H).
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11. Spectra data are shown below. **8:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.28 (m, 15 H), 5.89 (m, 1 H), 5.41 (ddd, $J$ = 17.2, 3.0, 1.8 Hz, 1 H), 5.25 (dd, $J$ = 10.4, 0.6Hz), 4.95 (d, $J$ = 10.8 Hz, 1 H), 4.85-4.76 (m, 3 H), 4.69-4.59 (m, 3 H), 4.08 (t, $J$ = 8.1 Hz, 1 H), 3.99 (t, $J$ = 9.3 Hz, 1 H), 3.53 (t, $J$ = 9.3 Hz, 1 H), 3.37 (s, 3 H), 3.25 (t, $J$ = 9.3 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.70, 138.09, 135.15, 128.39, 128.33, 128.29, 128.04, 127.95, 127.90, 127.84, 127.67, 127.58, 118.09, 98.00, 82.18, 81.63, 79.75, 75.80, 75.06, 73.33, 71.32, 55.13. **9:** IR (CHCl$_3$) 3004, 2915, 1727, 1453, 1360, 1071, 735, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.67 (dd, $J$ = 2.4, 1.6 Hz, 1 H), 7.37-7.24 (m, 15 H), 5.01 (d, $J$ = 10.8 Hz, 1 H), 4.91 (d, $J$ = 11.0 Hz, 1 H), 4.82 (d, $J$ = 7.6 Hz, 1 H), 4.79 (d, $J$ = 8.9 Hz, 1 H), 4.65 (d, $J$ = 12.1 Hz, 1 H), 4.56 (d, $J$ = 11 Hz, 1 H), 4.49 (d, $J$ = 3.6 Hz, 1 H), 4.18 (dt, $J$ = 9.8, 6.2 Hz, 1 H), 4.01 (t, $J$ = 9.2 Hz, 1 H), 3.51 (dd, $J$ = 9.7, 3.6 Hz, 1 H), 3.40 (s, 3 H), 3.24 (t, $J$ = 9.2 Hz, 1 H), 2.72 (ddd, $J$ = 16.2, 3.6, 1.6 Hz, 1 H), 2.43 (ddd, $J$ = 16.2, 9.0, 2.4 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 199.94, 138.48, 137.94, 137.73, 128.49, 128.44, 128.13, 128.06, 127.98, 127.70, 97.98, 81.82, 80.81, 79.96, 75.77, 75.04, 73.41, 65.54, 55.46, 45.76. **10 (major):** IR (CHCl$_3$) 3478, 3029, 2924, 1496, 1453, 1359, 1088, 735, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.24 (m, 35 H), 4.95 (d, $J$ = 10.8 Hz, 1 H), 4.90-4.73 (m, 3 H), 4.66-4.25 (m, 11 H), 4.15-4.08 (m, 2 H), 3.98-3.89 (m, 2 H), 3.85 (dd, $J$ = 4.8, 3.2 Hz, 1 H), 3.83-3.69 (m, 5 H), 3.49 (dd, $J$ = 9.7, 3.6 Hz, 1 H), 3.30 (s, 3 H), 3.24 (t, $J$ = 9.3 Hz, 1 H), 2.81 (d, $J$ = 5.1 Hz, 1 H), 2.01 (dt, $J$ = 14.2, 3.2 Hz, 1 H), 1.81 (dt, $J$ = 14.2, 8.9 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.65, 138.41, 138.28, 138.21, 138.12, 138.07, 128.45, 128.36, 128.32, 128.29, 128.09, 127.95, 127.88, 127.75, 127.61, 127.59, 127.54, 127.47, 97.95, 81.97, 81.80, 79.85, 77.20, 75.72, 75.61, 75.07, 74.72, 74.48, 73.39, 73.14, 72.98, 72.88, 72.48, 72.29, 71.84, 69.78, 68.76, 68.50, 55.39, 35.05; HRMS (FAB, +Cs$^+$) calcd for C$_{63}$H$_{68}$O$_{11}$Cs 1133.3816, found 1133.3860.
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