# Reactions of Glycosyl Fluorides. Synthesis of *O*-, *S*-, and *N*-Glycosides

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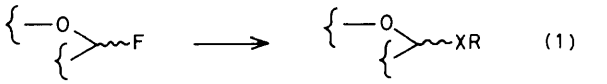
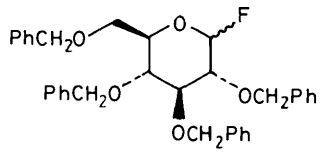
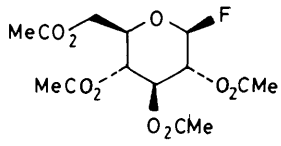
Glycosyl fluorides react with a variety of *O*-, *S*-, and *N*-nucleophiles to afford the corresponding glycosides in good to excellent yields.

The high abundance and biological importance of carbohydrate-containing natural products, such as *C*-glycosides, lipopolysaccharides, glycoproteins, and nucleotides dictate new synthetic technology for their construction. In previous papers we described reactions of glycosyl fluorides leading to *C*-glycosides[1] and oligosaccharides.[2,3] In this communication we report the utilization of these versatile intermediates in the synthesis of novel *O*-, *S*-, and *N*-glycosides, equation (1),†‡ all compounds of potential biological importance. Table 1 demonstrates the scope of this methodology with the preparation of glycosyl esters (entries 1,2,14), 'double' glycosides (entry 3), thioglycosides (entries 11,12), glycosyl peroxides (entry 6), glycosyl azides (entry 7), and aminoglycosides (entries 8—10). In most cases $BF_3{\cdot}Et_2O$ was found to be an effective catalyst for the coupling reaction. Amines were coupled to the carbohydrate residue after activation with $AlMe_3$ or by the action of $MgBr_2{\cdot}Et_2O$, which presumably leads to the more active glycosyl bromide as an intermediate.[1] The facile coupling of glycosyl fluorides to bases such as 6-azauridine *via* its disilyl ether after activation with $SnCl_4$ (entry 13)[4] offers promising applications of the present technology in the construction of nucleotides, whereas the entry into glycosyl phosphate esters (entry 4) may provide the first stage for stereospecific enzyme-induced glycosidations.[5] It is expected that the present methodology will find widespread applications in the synthesis of carbohydrate-containing naturally occurring and other synthetic molecules.




(1)

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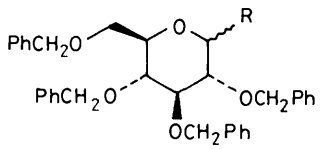


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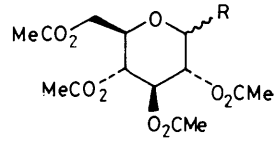
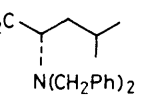



(4)

a; R = 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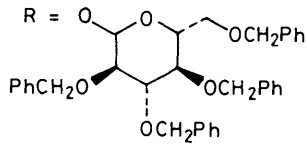
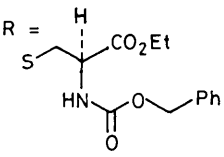
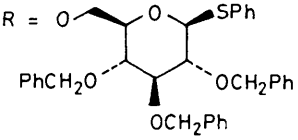
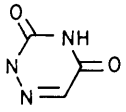
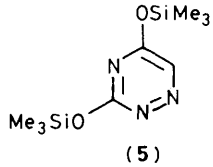
b; R = 

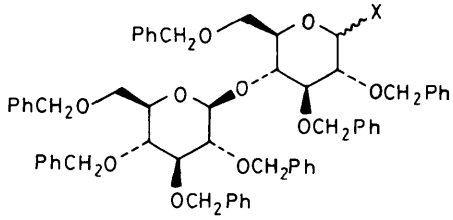

e; R = 


c; R = 


f; R = 


(5)




(6) X = F
(7) X = R (OCOMe)

† New compounds exhibited satisfactory spectroscopic and analytical data. Yields refer to pure isolated (flash column chromatography–silica) products.

‡ $^1$H N.m.r. data (250 MHz, $CDCl_3$, $Me_4Si$) (**2a**) δ 7.50—7.10 (m, 30H, Ph), 6.42 (d, *J* 4.5 Hz, 1-H), 4.97—4.52 (m, 8H, $OCH_2Ph$), 3.94—3.68 (m, 6H, CHO, $CH_2O$), 3.89 and 3.61 (doublets, *J* 15.0 Hz, 2H each, $NCH_2Ph$), 3.44 (dd, *J* 8.1, 6.9 Hz, 1H, $CHCO_2$), 1.84—1.45 (m, 3H, $CH_2CHMe_2$), 0.80 and 0.61 (doublets, *J* 7.5 Hz, 3H each, $CMe_2$); (**2d**) 7.50—7.20 (m, 20H, Ph), 5.00—4.55 (m, 8H, $CH_2Ph$), 3.93 (d, *J* 8.0 Hz, 1-H), 3.80—3.35 (m, 6H, CHO, $CH_2O$), 3.02—2.70 (m, 8H, morpholine); (**4e**) 7.40 (m, 5H, Ph), 5.90 (d, *J* 7.5 Hz, 1H, NH), 5.12 (m, 5H, 2-H, 3-H, 4-H, $OCH_2Ph$), 4.59 (m, 1H, $CHCO_2Et$), 4.48 (d, *J* 8.0 Hz, 1-H), 4.20 (m, 4H, 6-H, $OCH_2Me$), 3.63 (m, 1H, 5-H), 3.25 (dd, *J* 12.0, 4.5 Hz, 1H, $SCH_2$), 3.05 (dd, *J* 12.0, 5.0 Hz, 1H, $SCH_2$), 2.12, 2.08, 2.07, 2.05 (singlets, 3H each, OAc), 1.25 (t, *J* 5.0 Hz, 3H, $OCH_2Me$); (**4f**) 9.88 (br.s, 1H, NH), 7.51 (s, 1H, CH=N), 5.89 (d, *J* 7.5 Hz, 1H, 1-H), 5.69, 5.35, 5.15 (dd's, *J* 7.5 Hz, 1H each, 2-H, 3-H, 4-H), 4.20 (m, 2H, 6-H), 3.94 (m, 1H, 5-H), 2.14, 2.12, 1.99, 1.94 (singlets, 3H each, OAc).

**Table 1.** Synthesis of O-, S-, and *N*-glycosides.

| Entry | Reagents (equiv.) and conditions | R | Yield ratio α:β)[f] |
|---|---|---|---|
| Substrate (**1**)[a,b,c] → product (**2**).[b] | | | |
| 1 | $MeCO_2H$ (4), $BF_3{\cdot}Et_2O$ (0.5), $CH_2Cl_2$, 4Å MS,[d] 0→25 °C | Me | 97 (*ca.* 3 : 2) |
| 2 | RH (2), $BF_3{\cdot}Et_2O$ (0.3), $CH_2Cl_2$, 4Å MS, 0 °C | (**a**) | 76 (10 : 1) |
| 3 | RH (1), $BF_3{\cdot}Et_2O$ (0.3), $CH_2Cl_2$, 0→25 °C | (**b**) | 65[e] |
| 4 | $(PhCH_2O)_2P(O)OSnBu^n_3$ (2), $BF_3{\cdot}Et_2O$ (2), $Et_2O$, 0→25 °C | $O(O)P(OCH_2Ph)_2$ | 50 (10 : 1) |
| 5 | RH (1), $BF_3{\cdot}Et_2O$ (0.5), 4Å MS, −15→0 °C | (**c**) | 51 (2 : 1) |
| 6 | $Bu^tO_2H$ (2), $BF_3{\cdot}Et_2O$, (0.2), $CH_2Cl_2$, 4Å MS, −15→0 °C | $O_2Bu^t$ | 91 (3 : 1) |
| 7 | $Me_3SiN_3$ (2.5), $BF_3{\cdot}Et_2O$ (0.5), $CH_2Cl_2$, 0→25 °C | $N_3$ | 90 (10 : 1) |
| 8 | RH (1.5), $MgBr_2{\cdot}Et_2O$ (5), $CH_2Cl_2$, 25 °C | (**d**) | 90 (1 : 10) |
| 9 | $H_2NCH_2{=}CH_2$ (1), $AlMe_3$ (1), $CH_2Cl_2$, 25 °C | $NHCN_2CH{=}CH_2$ | 95 (2 : 1) |
| 10 | $H_2NPh$ (2), $AlMe_3$ (2), $CH_2Cl_2$, 25 °C | NHPh | 65 (1 : 1) |
| Substrate (**3**)[a,b] → product (**4**).[b] | | | |
| 11 | RH (1.5), $BF_3{\cdot}Et_2O$ (0.1), $CH_2Cl_2$, 25 °C | (**e**) | 80 (1 : 20) |
| 12 | PhSH (2), $BF_3{\cdot}Et_2O$ (0.1), $CH_2Cl_2$, 25 °C | SPh | 95 (1 : 20) |
| 13 | (**5**) (1.5), $SnCl_4$ (0.2), $CH_2Cl_2$, 25 °C | (**f**) | 76 (1 : 20) |
| Substrate (**6**)[a,b,c] → product (**7**).[b] | | | |
| 14 | $MeCO_2H$ (4), $BF_3{\cdot}Et_2O$ (0.5), $CH_2Cl_2$, 4Å MS, 0→25 °C | OCOMe | 83 (3 : 2) |

[a] Prepared from the corresponding phenylthioglycoside and *N*-bromosuccinimide–diethylamino sulphur trifluoride (ref. 2); [b] structure determined by spectroscopic methods; [c] α:β mixture *ca.* 1:1; [d] MS = molecular sieve; [e] ratio not determined; [f] ratio was determined by $^1H$ n.m.r.

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