O-Glycosylation in the Solid to Solid State

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Glycosylation in the solid to solid state produced glycosides in a simple, mild and stereoselective fashion, and this methodology could serve as an addition to existing glycosylation procedures.

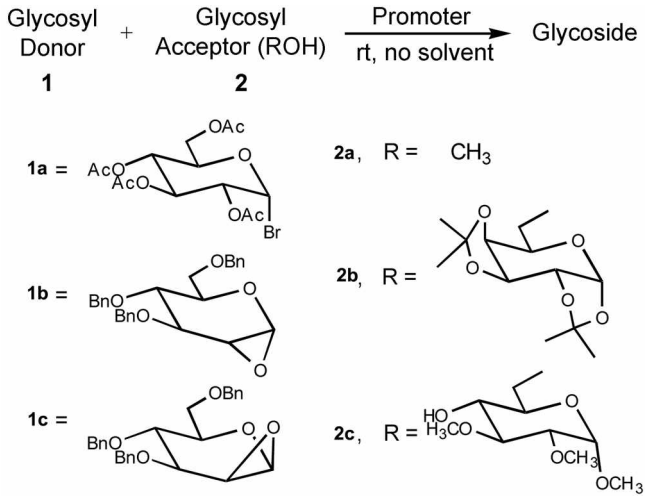
A large number of efficient glycosylation procedures have been developed; most of these protocols are being carried out in solution.[1] However, there is still a continuing demand for an appreciable process in terms of mildness, efficacy and stereocontrol.

In our earlier work,[2] we demonstrated that *N*-glycosylation in the solid to solid state provided glycopyranosyl-uracil or -thymine with an enhancement in selectivity, and that this method could serve as a viable alternate to existing solutions and/or fusion procedures. Extending of this methodology, we now report that *O*-glycosylation in the solid to solid state produced glycoside with excellent stereoselectivity. The glycosylation was simply produced by grinding the glycosyl donor and acceptor in the presence of the promoter with a mortar and pestle for 30 min under argon atmosphere in a glove box. When necessary, the reaction mixture was further ground in a ball mill for 24 hr. The results of *O*-glycosylation obtained from the solution, and present methods for the comparison between the two are summarized in the Table 1.

Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1a**, 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **1b**[3] and 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose **1c**[4] used as glycosyl donors, and methanol **2a**, 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose **2b** and methyl 2,3-di-*O*-methyl-α-D-glucopyranoside **2c** used as the glycosyl acceptor are shown in the following Scheme 1.

Because of its high hygroscopic nature and the difficulty of handling of **1a** due to moisture present in the air, we also tested **1b** and **1c** as the glycosyl donor instead of **1a** in this study. We found these 1,2-anhydrosugars gave better results in the formation of a disaccharide with greatly reduced reaction times and enhanced yields of product. Thus, the reaction of **1b** with **2c** in the solid to solid state for 30 min produced 43% of glucoside, while the same reaction in solution for 20 hr produced only 35% of the product.

In the presence of Amberlite IRC-50, a cationic form of ionic exchange resin, and in the absence of promoter, **1b** also reacted with **2c** and formed the corresponding disaccharide,



Scheme 1. *O*-Glycosylation of various acceptors with donors in the solid to solid state.

producing 32% and 18% of product, respectively. When liquid acceptor **2a** and a solution of **2b** in $CHCl_3$ were added to the ground mixture of **1b** and an activator, glycosylation also proceeded. These observations clearly demonstrate that solid to solid state methodology could be widely extended in glycosylation.

In summary, although there is still room for improvement in yield of the product, the solid to solid state reaction methodology could effectively serve as a simple, mild, and stereoselective procedure in glycosylation.

Experimental Section

General procedure for glycosylation in the solid to solid state 1b-2c: To a mixture of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (**1b**, 107 mg, 0.247 mmol), methyl 2,3-di-*O*-methyl-α-D-glucopyranose (**2c**, 55 mg, 0.25 mmol), and $ZnCl_2$ (3 mg, 0.022 mmol) was ground with a mortar and pestle at room temperature for 30 min under argon atmosphere in a glove box. After quenching the reaction by the addition of water, $CHCl_3$ was added. The reaction mixture was filtered and extracted with $CHCl_3$. Then combined extracts were concentrated *in vacuo* and the residue was chromatographed (Silica gel 60, Ethyl acetate: n-Hexane/3:1) to produce 70.1 mg of disaccharide (43%) as well as 60.0 mg of 3,4,6-tri-*O*-benzyl-α/β-D-glucose (55%).

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Table 1. *O*-Glycosylation in the solid to solid state

Substrate	Reactant	Method	Activator[a]	Product[b]	Yield[c] (%)	Ratio (a:b)[c]
1a	**2b**	solid	A	**1a-2b**[5]	29	β
	2b	solution[d]	A	**1a-2b**	19	β
	2c	solid	A	**1a-2c**	21	β
	2c	solution[d]	A	**1a-2c**	65	β
1b	**2a**	solid[e]	B	**1b-2a**[6]	99	β
	2b	solid[f]	B	**1b-2b**[7]	37	β
	2b	solution[g]	B	**1b-2b**	21	β
	2c	solid	B	**1b-2c**	43	β
	2c	solution[g]	B	**1b-2c**	35	β
	2c	solid	C	**1b-2c**	32	β
	2c	solid	D	**1b-2c**	18	β
1c	**2b**	solid	B	**1c-2b**[7]	33	α
	2b	solution[g]	B	**1c-2b**	26	α
	2c	solid	B	**1c-2c**	35	α
	2c	solution[g]	B	**1c-2c**	39	α

[a]A, $AgOCOCF_3$; B, $ZnCl_2$; C, Amberlite IRC-50, H^+ form; D, no activator but MS4Å. [b]All products gave satisfactory ^{1}H- and ^{13}C-NMR spectra. [c]Determined after isolation. [d]The reaction was performed in CH_2Cl_2 at −78 °C for 3 hr, then stirred at rt for 3 hr. [e]After substrate and activator were ground with a mortar and pestle for 20 min, one drop of liquid acceptor was added then the mixture was further ground for an additional 20 min. [f]After substrate **1b** and activator were ground in an agate mortar for 20 min, one drop of solution containing **2b** in $CHCl_3$ was added, and the resulting mixture was ground for an additional 20 min. [g]Reaction was performed in THF at −78 °C for 2 hr, then stirred at rt for 24 hr.[7]

General procedure for glycosylation in solution state 1c-2c: A solution of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (**1c**, 38.5 mg, 0.089 mmol) and methyl 2,3-di-*O*-methyl-α-D-glucopyranose (**2c**, 31.7 mg, 0.143 mmol) in THF (0.30 mL) was stirred at −78 °C, then 0.2 M $ZnCl_2$ in diethyl ether(0.75 mL, 0.022 mmol) was added and stirred at −78 °C for 2 hr and allowed to warm over 1 hr to rt. After stirring at rt for 24 hr. The reaction mixture was quenched by the addition of water, $CHCl_3$ was added. The reaction mixture was filtered and extracted with $CHCl_3$. Then combined extracts were concentrated in vacuo and the residue was chromatographed (Silica gel 60, Ethyl acetate:*n*-Hexane /3:1) to produce 22.73 mg of disaccharide (39%).

Disaccharide 1a-2c (Table 1): mp: 53-55 °C; $[\alpha]_D^{20}$: 45.6° (c = 5.0 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.0 (m, 12H), 2.55 (b, OH), 3.3-3.6 (m, 9H), 4.6 (d, J = 7.7 Hz, 1H, C_1-H), 4.8 (d, 1H, C'_1-H); ^{13}C-NMR ($CDCl_3$): δ 170.8, 170.3, 169.4, 169.3, 101.0, 97.34, 82.6, 81.7, 72.7, 71.8, 71.1, 70.6, 69.9, 68.6, 68.3, 61.8, 61.2, 58.5, 55.2, 20.75, 20.70, 20.62; Anal. Calcd for $C_{23}H_{36}O_{15}$: C, 50.00; H, 7.03. Found: C, 49.96; H, 6.92.

Disaccharide 1b-2c (Table 1): Syrup; $[\alpha]_D^{20}$: 47.8° (c = 3.20 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.7 (br, 2H), 3.25 (dd, 1H), 3.43 (s, 3H), 3.49 (s, 3H), 3.64 (s, 3H), 3.33-3.90 (m, 9H), 4.17 (dd, 1H), 4.36 (m, 1H), 4.40-4.60 (m, 3H), 4.67 (d, J = 8.37 Hz, 1H, C_1-H), 4.78-4.97 (m, 4H), 7.13-7.35 (m, 15H, aromatic); ^{13}C-NMR ($CDCl_3$): δ 138.5, 138.0, 137.9, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 103.4, 97.5, 84.5, 82.7, 81.7, 77.2, 75.19, 75.0, 74.4, 73.5, 70.5, 69.9, 69.2, 68.8, 61.3, 58.6, 55.3; Anal. Calcd for $C_{33}H_{46}O_{11}$: C, 66.04; H, 7.08. Found: C, 65.96; H, 6.98.

Disaccharide 1c-2c (Table 1): Syrup; $[\alpha]_D^{20}$: 50.9° (c = 1.35 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.3 (br, 2H), 3.23 (dd, 1H), 3.40 (s, 3H), 3.51 (s, 3H), 3.63 (s, 3H), 3.41-3.9 (m, 8H), 4.08 (dd, 1H), 4.14 (1H), 4.42 (t, 1H), 4.44-4.83 (m, 6H, $BnCH_2$), 4.86 (d, J = 3.5 Hz, 1H, C'_1-H), 4.95 (d, J = 1.38 Hz, 1H, C_1-H), 7.10-7.35 (m, 15H, aromatic); ^{13}C-NMR ($CDCl_3$): δ 137.9, 137.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 99.3, 97.5, 82.9, 81.6, 80.2, 75.2, 74.3, 73.3, 72.0, 71.3, 70.1, 69.4, 68.7, 68.3, 56.7, 61.3, 58.7, 55.2; Anal. Calcd for $C_{36}H_{46}O_{11}$: C, 66.04; H, 7.08. Found: C, 65.96; H, 7.12.

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