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GLYCOSIDATION OF SOLID-SUPPORTED GLYCOSYL DONORS TETHERED BY A TRIALKYLSILANE LINKER

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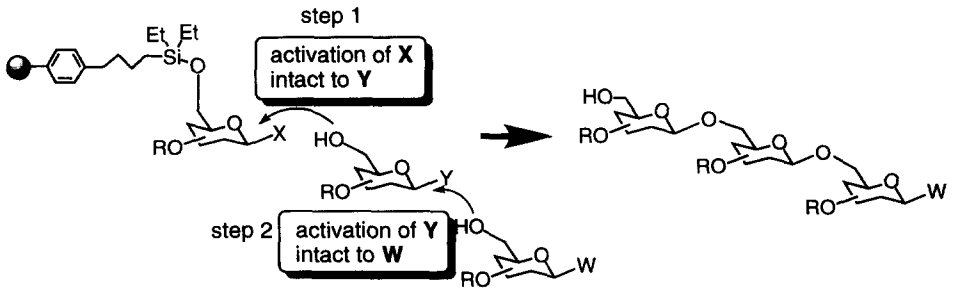
Abstract: *Glycosidation of silicon-connected glycosyl donors on polystyrene resin is described. Thiophenyl glycoside* ***2a*** *and glucopyranosyl fluoride* ***2b*** *reacted with glycosyl acceptor 3 (R^2 = Bn) to give disaccharide* ***4a*** *in 96% and 70% yields, respectively. Glycosidation of thiophenyl glucoside* ***2a*** *(R^1 = Bn or Bz) with glycosyl acceptor 3 (R^2 = Bn or Ac) yielded* ***4a-4c*** *in satisfactory yields and* ***4d*** *in moderate yield.*

Keywords: Glycosidation; Solid-phase synthesis; Thioglycosides; Resins

Solid phase synthesis is a powerful tool for preparing libraries of compounds for bioactive target molecules, especially in the field of oligopeptides and oligonucleotides. However, the solid phase synthesis of oligosaccharides[1-3] and oligosaccharide libraries[4] has been considerably more challenging which has thwarted efforts towards fully automated synthesis. Recently, Danishefsky *et al.* demonstrated that a silicon-connected linker may be employed in the solid phase synthesis of oligosaccharides using a glucal-activation method under mild, neutral conditions.[5] However, it still remains to be shown whether silicon linkers are chemically stable to the various acid-promoted glycosidation conditions.[6] It would be helpful for the solid phase synthesis of oligosaccharides if the conditions the silicon linker can endure among numerous glycosidation conditions could be established, along with the proper combination of glycosyl acceptor and Lewis acid required. Our concept, a one-pot sequential glycosidation, reported as a solution phase version,[7] could also be useful on the solid phase without transformation of functional groups, such as deprotection (Figure). Herein, we wish to report the glycosidation of solid-supported glycosyl donors linked to the polymer backbone with a trialkylsilane linker.

Figure Sequential Synthesis of Oligosaccharides on Solid Phase by Utilizing a One-Pot Glycosidation.



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PS-DES resin (Argonaut Technologies, 0.75 mmol/g) was used after chlorination by 1,3-dichloro-5,5-dimethylhydantoin (0.3 M in CH_2Cl_2).[8] Glycosyl donors **1a-d** (R^1 = Bn) with a benzoyl group at the 2-position (for the exclusive formation of β-glycoside) were loaded onto the silyl chloride resin in the presence of imidazole in dichloromethane (Scheme 1). After washing three times with CH_2Cl_2, DMF, THF / H_2O (4 : 1), methanol and CH_2Cl_2, the resin was dried *in vacuo*. The loading yields of the glycosyl donors **2a-d** (R^1 = Bn) were determined to be 39%, 40%, 30%, and 54%, respectively, after cleavage from the solid support. Glycosidation of **2a-d** (R^1 = Bn) with 10 equiv. of **3** (R^2 = Bn) was carried out in the presence of Lewis acid

Scheme 1

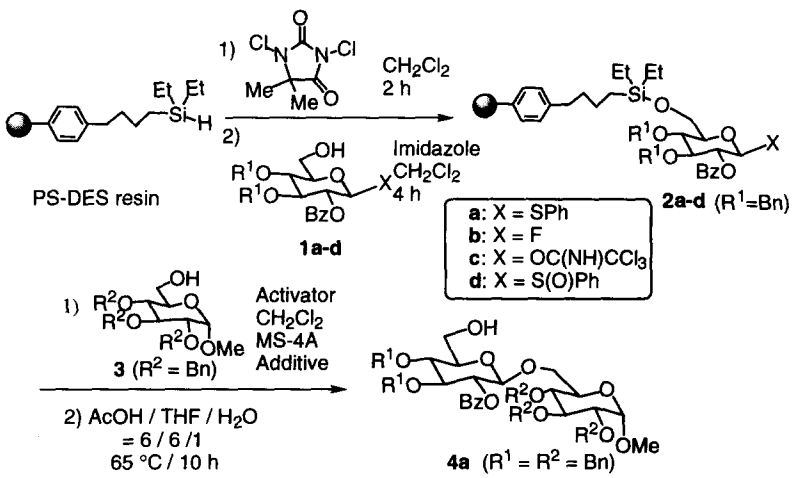

Table 1 Glycosidation of Polymer-Supported Various Glycosyl Donors

Entry	X	Activator	Additive	Yield[g] / %	Purity[h] / %
1	β–SPh[a]	DMTST	DTBP	quant	93
2		NIS / TfOH	DTBP	quant	96
3		DMTST	-	-	-
4		NIS / TfOH	-	-	-
5	α, β - F[a]	$Cp_2Hf(OTf)_2$	DTBP / TMSOMe	quant	64[i]
6	(α : β = 1)	$Cp_2Hf(OTf)_2$	DTBP	90	78[j]
7		$Cp_2Hf(OTf)_2$	-	-	-
8	α, β –OC(NH)CCl_3[a,b]	TfOH	DTBP	95	69[k]
9		$BF_3{\cdot}OEt_2$	DTBP	70	70[k]
10		TfOH	-	47	76[k]
11		$BF_3{\cdot}OEt_2$	-	59	50[k]
12	β-S(O)Ph[c]	Tf_2O[d]	DTBP	quant	m
13		TMSOTf / $P(OEt)_3$[e]	DTBP	quant	m
14		TfOH / MP[f]	DTBP	quant	m
15		TMSOTf / $P(OEt)_3$	-	quant	m
16		TfOH / MP	-	quant	m

[a] Glycosidation was carried out at room temperature for 12 h. [b] Trichloroacetimidate was prepared from **2** (X = OH) (2 equiv DBU, 10 equiv Cl_3CCN, CH_2Cl_2, r.t.). [c] Glycosidation was carried out at -78 °C to r.t. for 12 h. [d] ref 14. [e] ref 15. [f] ref 16. [g] Yield was determined by the weight of the crude product after acid cleavage. [h] Purity was determined by HPLC analysis. [i] α-Fluoride of **1b** was recovered in 17% yield. [j] α-Fluoride **1b** was recovered in 10% yield. [k] The hydrolized product **1** (R^1 = Bn, X = OH) was also observed. [m] Unreacted sulfoxide was fully recovered after acid cleavege. DMTST = dimethyl(methylthio)sulfonium triflate; DTBP = 2,6-di-*tert*-butyl pyridine; MP = methyl propiolate.

with or without base additive. After reaction, the resins were washed with solvents mentioned above several times and cleaved using AcOH / THF/ H_2O (6 / 6 / 1, 65 ℃, 10 h). Reaction mixtures were concentrated, and the yield and the purity of the desired disaccharide **4a** was determined by HPLC. The results are given in Table 1. Thiophenyl glycoside **2a** was effective as a glycosyl donor with the relatively active glycosyl acceptor **3** (R^2 = Bn) in the presence of 2,6-di-*tert*-butyl pyridine (DTBP) to give **4a** in quantitative yield (Entries 1 and 2 in Table 1). HPLC analyses of the crude product obtained by both activators, dimethyl(methylthio)sulfonium triflate (DMTST)[9] and *N*-iodosuccinimide (NIS) / trifluoromethanesulfonic acid (TfOH),[10] gave 93 and 96% purities, respectively. Glucopyranosyl fluoride **2b** (α-fluoride : β-fluoride = 1 : 1) underwent glycosidation in the presence of $Cp_2Hf(OTf)_2$[11] and DTBP to afford the disaccharide in good yield. The purity of the product **4a** was inferior to the product obtained in the glycosidation of thiophenyl glycoside because unreacted α-fluoride of **1b** was also recovered (Entries 5 and 6). In the absence of DTBP, polymer-supported glycosyl donors were cleaved from the resin under glycosidation conditions (Entries 3, 4, and 7).[12] Glycosidation using trichloroacetimidate **2c**[13] as the glycosyl donor also gave the disaccharide in better yield in the presence of DTBP (Entries 8-11). However, the purity of the product reached a maximum of 70% due to the hydrolized product of the imidate. Sulfoxide **2d** did not undergo glycosidation[14-16] on the solid phase in our hands for this particular substrate (Entries 12-16) although the glycosidation of a polymer-supported glycosyl acceptor has been successfully reported by Kahne.[17]

Since thiophenyl glycoside **2a** is the optimal glycosyl donor as shown in Table 1, the glycosidation of an armed- or a disarmed-thioglycoside with an armed- or a disarmed-glycosyl acceptor was next examined.[18] The results are given in Table 2. When either the glycosyl donor or acceptor is armed by benzyl ether protection, the glycosidation on solid phase proceeded well to provide the desired disaccharide in good yield. However, when both substrates are disarmed by electron-withdrawing protective groups, such as benzoates and acetates, the yield of the disaccharide was less than 41% because of the lower reactivity of the combination of both glycosyl donors and acceptors.

Scheme 2

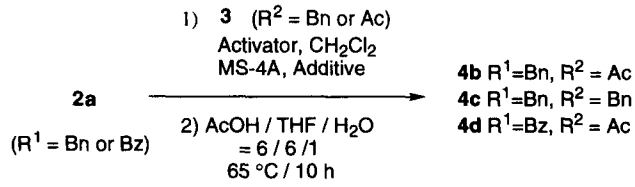

Table 2 Glycosidation of Polymer-Supported Armed- or Disarmed Thiophenyl Glycosides

Entry[a]	R^1	R^2	Activator	Additive	Product	Yield[b] / %	Purity[c] / %
1	Bn	Ac	DMTST	DTBP	**4b**	quant	70
2			NIS / TfOH	DTBP		quant	85
3	Bz	Bn	DMTST	DTBP	**4c**	quant	78
4			NIS / TfOH	DTBP		quant	81
5	Bz	Ac	DMTST	DTBP	**4d**	96	41[d]
6			NIS / TfOH	DTBP		97	22[d]

[a] All reactions were carried out at room temperature for 12 h. [b] Yield was determined by the weight of the crude product after acid cleavage. [c] Purity was determined by HPLC analysis. [d] By-products are not structure-determined.

In conclusion, we have demonstrated that the glycosidation of solid-supported glycosyl donors may be carried out using a trialkylsilane resin (PS-DES), and both thiophenyl glycosides and β-glucopyranosyl fluorides were found to be compatible with this linker and the most effective glycosyl donors in solid-phase glycosidation. Further studies, including the synthesis of oligosaccharide libraries, are ongoing in our laboratories and will be reported in due course.

REFERENCES AND NOTES

1. Fréchet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492-496; Fréchet, J. M.; Schuerch, C. *Carbohydrate Res.* **1972**, *22*, 399-412.
2. Guthrie, R. D.; Jenkins, A. D.; Stehleícek, J. *J. Chem. Soc. (C)* **1971**, 2690-2696; Guthrie, R. D.; Jenkins, A. D.; Roberts, G. A. F. *J. Chem. Soc. Perkin I* **1973**, 2414-2417.
3. Belorizky, N.; Excoffier, G.; Gagnaire, D.; Utille, J. P.; Vignon, M.; Vottero, P. *Bull. Soc. Chim. France* **1972**, 4749-4753; Excoffier, G.; Gagnaire, D.; Utille, J. P.; Vignon, M. *Tetrahedron Lett.* **1972**, 5065-5068.
4. Liang, R.; Yan, L.; Loebach, J.; Ge, M.; Uozumi, Y.; Sekanina, K.; Horan, N.; Gildersleeve, J.; Thompson, C.; Smith, A.; Biswas, K.; Still, W. C.; Kahne D. *Science* **1996**, *274*, 1520-1522.
5. Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B. *Science* **1993**, *260*, 1307-1309; Randolph, J. T.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5712-5719.
6. During this work, successful glycosidation of thioethyl glycosides was reported on diisopropylsilylated polystyrene resin activated by methyl triflate in the presence of DTBP. See: Zheng, C.; Seeberger, P. H.; Danishefsky, S. J. *J. Org. Chem.* **1998**, *63*, 1126-1130.
7. Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919-7920.
8. Hu, Y; Porco, Jr., J. A.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518-4521.
9. Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, 9-12.
10. Veenemam, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331-1334.
11. $Cp_2Hf(OTf)_2$ was prepared *in situ* from 1 : 2 Cp_2HfCl_2 - AgOTf; see: Ikeshita, S.; Sakamoto, A.; Nakahara, Y.; Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1994**, *35*, 3123-3126; Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567-3578.
12. Silicon-linkages are stable under glycosidation conditions in the presence of DTBP, see: Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247-248; Martichonok, V.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 8187-8191; Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064-10072; see: ref 6.
13. Schmidt, R. R.; Michel, J. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 731-732.
14. Kahne, D; Walker, S.; Cheng, T.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881-6882.
15. Sliedregt, L. A. J. M.; van der Marel, G. A.; Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015-4018.
16. Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580-1581.
17. Yan, L.; Taylor, C. M.; Goodnow, R., Jr.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6953-6954.
18. Mootoo, D. R.; Konradsoon, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583-5584; Fraser-Reid, B.; Udodong, U.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927-942.