Direct Glycosylations with 1-Hydroxy Glycosyl Donors using Trifluoromethanesulfonic Anhydride and Diphenyl Sulfoxide

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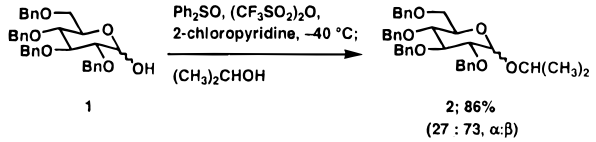
Received April 4, 1997

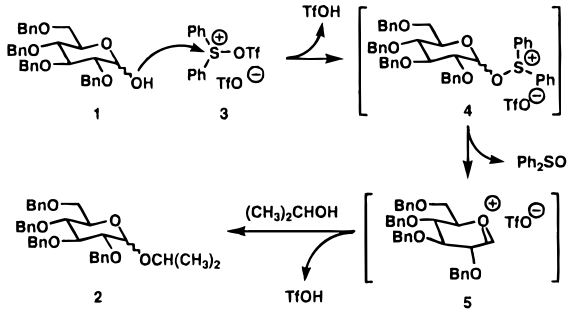
Considerable effort has been devoted to the development of new methods for glycosidic coupling due to the growing importance of synthetic oligosaccharides in glycobiology.[1] The synthesis of complex oligosaccharides and glycoconjugates has traditionally employed multistep glycosylation protocols involving (1) functionalization of the anomeric hydroxyl to form an isolable glycosyl donor and (2) reaction of the donor with a promoter or catalyst to induce irreversible carbohydrate transfer to a nucleophilic acceptor.[2] However, a direct substitution of the glycosyl anomeric hydroxyl with the desired acceptor offers a potentially more efficient strategy for glycosylation as this obviates the need for anomeric derivatization prior to the coupling event.[3] We now report a new method for glycosidic bond construction directly from the free hemiacetal of the glycosyl donor. This one-step procedure is applicable to the glycosylation of a wide range of acceptors and involves the *in situ* activation of 1-hydroxy glycosyl donors with trifluoromethanesulfonic anhydride and diphenyl sulfoxide.

The facility of this protocol is exemplified by direct glycosylation with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**),[4] employing isopropyl alcohol as a model glycosyl acceptor (Scheme 1). In this representative procedure, trifluoromethanesulfonic anhydride (1.4 equiv) was added to a solution of **1** (1 equiv) and diphenyl sulfoxide (2.8 equiv) in a mixture of toluene and dichloromethane (3:1) at −78 °C.[5] The reaction mixture was stirred at −40 °C for 1 h, and the acid scavenger 2-chloropyridine[6] (5 equiv) and the glycosyl acceptor isopropyl alcohol (3 equiv) were then added sequentially at this temperature. The solution was stirred at 0 °C for 15 min and then at 23 °C for 1 h before the addition of excess triethylamine[7] (8 equiv).

Scheme 1



Scheme 2



Aqueous workup of the reaction mixture followed by silica gel column chromatography afforded isopropyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**2**)[8] in 86% yield (27:73; α:β).[9]

A proposed mechanism for this transformation (Scheme 2) involves initial activation of diphenyl sulfoxide with trifluoromethanesulfonic anhydride to form diphenyl sulfide bis(trifluoromethanesulfonate) (**3**).[10] *In situ* activation of the hemiacetal hydroxyl function in **1** by **3** would afford the oxosulfonium trifluoromethanesulfonate **4**, which can expel diphenyl sulfoxide[11] to generate the glycosyl oxocarbenium trifluoromethanesulfonate **5**. Reaction of **5** with isopropyl alcohol would then afford the isopropyl glucopyranoside **2**.[12]

To illustrate the scope of this direct dehydrative glycosylation method, a variety of acceptors in addition to isopropyl alcohol were coupled with **1** (Table 1). Oxygen, sulfur, carbon, and nitrogen nucleophiles were all found to be suitable glycosyl acceptors using this protocol. For example, phenol, ethanethiol, and 1,3,5-trimethoxybenzene underwent efficient glycosylation with **1** to yield the corresponding *O*-aryl-,[13] *S*-alkyl-,[14] and *C*-aryl-glycosides[15] in good yield (89%, 84%, 81%; entries 1−3). In addition, the *N*-glycosylation of amide functionalities, which has been reported to occur with only the most reactive of nonenzymatic glycosylation procedures,[16] was found to proceed smoothly with **1** and *N*-(trimethylsilyl)trimethylacet-

(1) (a) *Synthetic Oligosaccharides. Indispensable Probes for the Life Sciences*; Kovac, P., Ed.; ACS Symposium Series 560; American Chemical Society: Washington, DC, 1994. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.

(2) Many synthetically valuable anomeric functional groups have been developed in this context. General Reviews: (a) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, Inc.: New York, 1997. Chapters 12−22. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (c) Sinaÿ, P. *Pure Appl. Chem.* **1991**, *63*, 519. (d) Glycal donors: Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (e) Trichloroacetimidate donors: Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

(3) (a) Fischer, E. *Chem. Ber.* **1893**, *26*, 2400. (b) Koto, S.; Sato, T.; Morishima, N.; Zen, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1761. (c) Susaki, H. *Chem. Pharm. Bull.* **1994**, *42*, 1917. (d) Suda, S.; Mukaiyama, T. *Chem. Lett.* **1991**, 431. (e) Uchiro, H.; Mukaiyama, T. *Chem. Lett.* **1996**, 79, and references therein. (f) Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1090.

(4) Perrine, T. D.; Glaudemans, C. P. J.; Ness, R. K.; Kyle, J.; Fletcher, H. G., Jr. *J. Org. Chem.* **1967**, *32*, 664.

(5) Glycosylations performed in toluene did not proceed to completion due to incomplete solubility of **1** at −78 °C to −40 °C. Reactions performed in CH_2Cl_2 were generally not as efficient, leading to lower yields (60−70%). The preparation of **2** in toluene, CH_2Cl_2, and propionitrile led to similar α:β selectivity.

(6) The use of 2,6-lutidine as the acid scavenger led to diminished yields, presumably a result of its reactivity toward the electrophilic reactive intermediates formed in the reaction pathway (Scheme 2). The use of 2-chloropyridine avoided this problem. See: Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem Soc.* **1997**, *119*, 6072.

(7) The addition of excess triethylamine serves to neutralize 2-chloropyridinium trifluoromethanesulfonate prior to aqueous workup.

(8) Briner, K.; Vasella, A. *Helv. Chim. Acta* **1989**, *72*, 1371.

(9) Yields were determined by isolation of the mixture of anomeric products after silica gel chromatography. Trehalose-linked disaccharides arising from self-coupling of the hemiacetal donor were not detected. Anomeric ratios were determined by ^{1}H NMR analysis. Analytical samples of each anomer were obtained by preparative TLC or HPLC and did not exhibit anomeric epimerization when resubjected to the glycosylation reaction conditions.

(10) Activation of *dimethyl* sulfoxide with trifluoromethanesulfonic anhydride has been employed in Swern-type oxidations, sulfilimine synthesis, and quinone methide generation: (a) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, 273. (b) Coburn, M. D.; Hayden, H. H. *Synthesis* **1986**, 490. (c) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202.

(11) Glycosidic bond formation via direct displacement of Ph_2SO in **4** by the acceptor may also be a contributing pathway. Alkoxy *dimethyl*sulfonium ions have been shown to be susceptible to nucleophilic attack resulting in displacement of DMSO: Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1579.

(12) Attempts at the direct triflation of **1** in the absence of diphenyl sulfoxide (Tf_2O, 2,6-lutidine or 2-chloropyridine, −78 °C to 20 °C) followed by addition of isopropyl alcohol did not afford **2**.

(13) Briner, K.; Vasella, A. *Helv. Chim. Acta* **1990**, *73*, 1764.

(14) (a) Dasgupta, F.; Garegg, P. J. *Acta Chem. Scand.* **1989**, *43*, 471. (b) Li, Z.; Liu, P.; Qiu, D.; Cai, M. *Synth. Commun.* **1990**, *20*, 2169.

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(16) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

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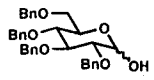
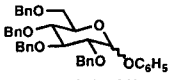
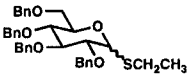
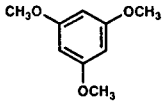
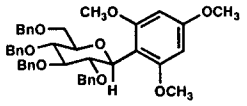
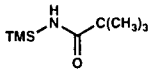
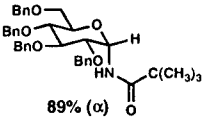
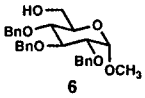
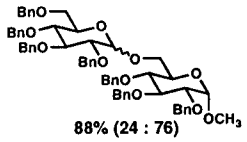
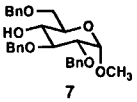
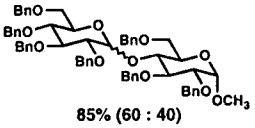
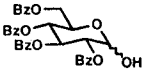
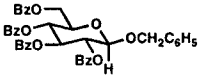
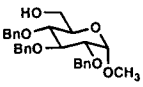
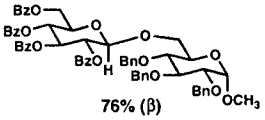
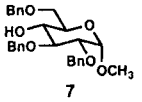
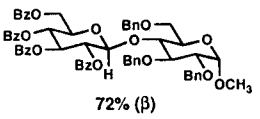
Table 1. Glycosylations with Trifluoromethanesulfonic Anhydride and Diphenyl Sulfoxide

Glycosyl Donor	Entry	Glycosyl Acceptor	Product: Yield (α:β)[a]
 **1** (Bn = benzyl) (α:β = 70 : 30)	1[b]	C_6H_5OH	 89% (78 : 22)
	2[b]	CH_3CH_2SH	 84% (83 : 17)
	3[c]		 81% (β)
	4[b]		 89% (α)
	5[d]	 **6**	 88% (24 : 76)
	6[d]	 **7**	 85% (60 : 40)
 **8** (Bz = benzoyl) (α:β = 88 : 12)	7[b]	$C_6H_5CH_2OH$	 71% (β)
	8[d]	 **6**	 76% (β)
	9[d]	 **7**	 72% (β)

[a] Anomeric ratios determined by ^{1}H NMR analysis. [b] 3 equiv of glycosyl acceptor. [c] 5 equiv of glycosyl acceptor. [d] 1.6 equiv of glycosyl acceptor.

amide[17] to afford the corresponding glycosyl amide with complete α-selectivity (89% yield, entry 4). Of critical importance is the application of this glycosylation method to the construction of oligosaccharides. Thus, **1** was coupled with the carbohydrate acceptors methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**6**)[18] and the sterically hindered methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**7**)[19] to form the corresponding (1,6)- and (1,4)-linked disaccharides[20] in 88% and 85% yield, respectively (entries 5 and 6).

To determine whether C(2)-neighboring group effects would influence the glycosylation stereochemistry, 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose (**8**)[21] was also prepared as a donor. When **8** was coupled with benzyl alcohol (entry 7), benzyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside[22] was isolated in 71% yield as the sole product of glycosylation. The high β-selectivity was also observed when carbohydrate acceptors such as **6** and **7** were employed in the coupling with **8**, yielding exclusively the β(1,6)- and the β(1,4)-linked disaccharides,[20] respectively, with similar efficiency (entries 8 and 9). This stereoselectivity is consistent with neighboring group participation of the equatorial C(2)-acyl substituent to favor β-glycoside formation.[2] Moreover, these experiments illustrate for the first time a single-step dehydrative glycosylation method that is compatible with deactivated carbohydrate donors incorporating multiple electron-withdrawing protective groups.[3]

All of the glycosylations reported in Table 1 were carried out with the glycosyl donor as the limiting substrate. Although a large excess of the acceptor can be used (3−5 equiv; entries 1−4, and 7) to decrease reaction times, couplings can also be performed in good yield with a modest excess of the glycosyl acceptor (1.6 equiv; entries 5, 6, 8, and 9) when synthetically valuable coupling partners are employed. In each of these cases, the excess nucleophile can be recovered from the reaction mixture.

It is worth noting that the mechanism proposed in Scheme 2 involves the regeneration of diphenyl sulfoxide.[23] Efforts to synthesize and screen various sulfoxide reagents to effect catalytic turnover of the sulfoxide species as well as to determine the effect of various sulfoxide structures on α:β selectivity[24] are currently underway and will be reported in due course.

In summary, a new dehydrative glycosylation method is described, involving *in situ* activation of the anomeric hydroxyl with trifluoromethanesulfonic anhydride and diphenyl sulfoxide. This one-pot procedure allows for the construction of a wide variety of glycoconjugates directly from 1-hydroxy glycosyl donors.

Acknowledgment. Financial support from the Department of Chemistry at the University of Illinois at Urbana-Champaign is gratefully acknowledged.

Supporting Information Available: Experimental details and spectral/analytical data for the glycosylation products (11 pages). See any current masthead page for ordering and Internet access instructions.

JA971067Y

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(21) (a) Ness, R. K.; Fletcher, H. G., Jr.; Hudson, C. S. *J. Am. Chem. Soc.* **1950**, *72*, 2200. (b) Itoh, T.; Takamura, H.; Watanabe, K.; Araki, Y.; Ishido, Y. *Carbohydr. Res.* **1986**, *156*, 241.
(22) Helferich, W. *Chem. Ber.* **1956**, *89*, 314.
(23) Diphenyl sulfoxide was recovered in 89% in the preparation of **2**. The preparation of **2** with 0.3 equiv of diphenyl sulfoxide proceeded slowly, leading to low yields (<30%).
(24) The synthesis of **2** was also attempted with *dimethyl* sulfoxide. The yield of **2** was similar to that with diphenyl sulfoxide with an anomeric ratio of 1:1; however, the addition of isopropyl alcohol to the anomeric center proceeded much more slowly (23 °C, 18 h) in the reaction employing DMSO.