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Polymer-Supported Syntheses of Oligosaccharides: Using Dibutylboron Triflate to Promote Glycosylations with Glycosyl Trichloroacetimidates.

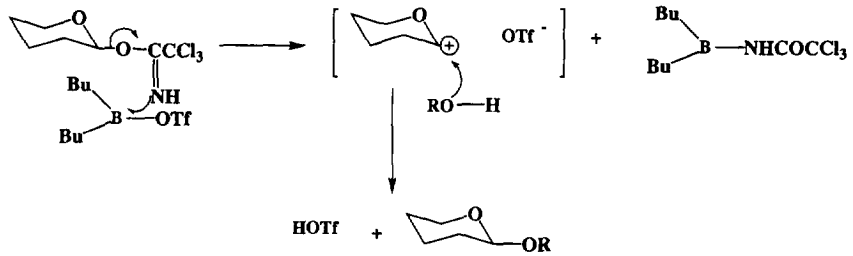
Zhi-Guang Wang, Stephen P. Douglas, and Jiri J. Krepinsky*

Department of Molecular and Medical Genetics, University of Toronto, Toronto, Ontario, Canada M5S 1A8

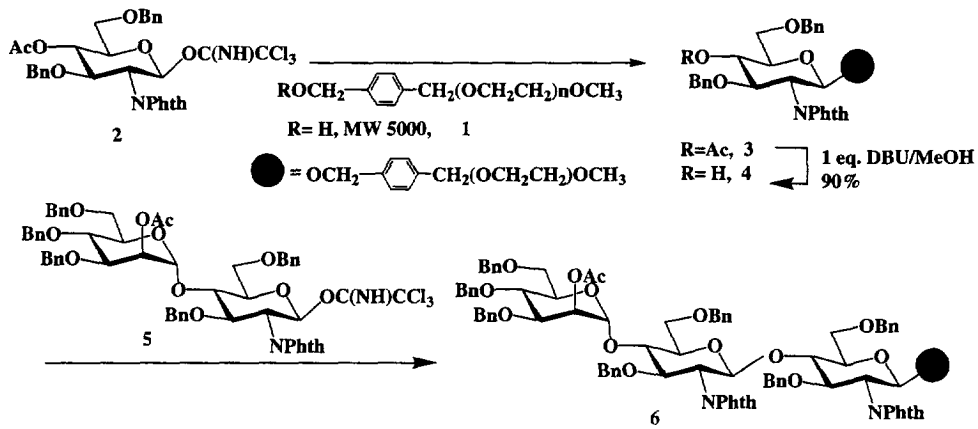
Abstract: Dibutylboron triflate as a promoter of glycosylations with glycosyl trichloroacetimidates compares favourably with most other promoters. Copyright © 1996 Published by Elsevier Science Ltd

Polymer supported synthesis of oligosaccharides[1] has recently undergone a resurrection from its dormant state in the early 1970's following the successful application of the exceptionally versatile glycosyl trichloroacetimidates as glycosyl donors.[2] Promoters such as boron trifluoride, the first Lewis acid used in this glycosylation type,[1,3] and derivatives of trifluoromethylsulfonic (triflic) acid such as silver triflate,[4] trimethylsilyl and triethylsilyl triflates[5] have proven effective in many cases but several problems have become exposed. BF_3-promoted reactions are often slow and incomplete, particularly with unreactive acceptors or donors. The alkylsilyl derivatives of triflic acid are more powerful but recent results in our and other laboratories have shown these to act as silylating reagents for unreactive or hindered hydroxyl groups. High yields (50% or more) of trialkylsilyl derivatives of the aglycon sometimes accompany the glycosylation reaction, which is particularly troubling for syntheses on polymeric support since overall yields are often lowered to unacceptable levels.[6] Therefore we have searched for a triflate which would act as a powerful promoter devoid of these undesirable properties.

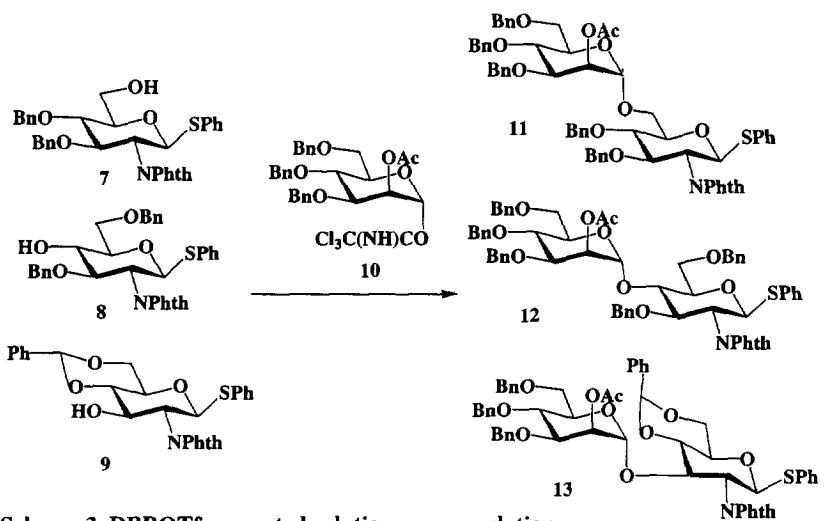
Considering the hypothetical mechanism of the promotion of glycosylation reactions with triflic acid and its derivatives, we estimated that a good promoter of this class must give easily the non-nucleophilic triflic anion and the electron-deficient activator (such as trialkylsilyl). The latter activator has to have sufficient affinity toward the imidate nitrogen for two reasons: (i) to bring about the electron shift leading to the formation of an electron-deficient anomeric carbon (whose charge must be counterbalanced by the non-nucleophilic triflic anion) and, (ii) to bind to the nitrogen tightly enough that this species would not rearrange and consequently become a competitive acceptor of the activated glycosyl donor. It appeared to us that commercially available dibutylboron triflate satisfies both above conditions (cf. Scheme 1). The dibutylboron moiety acts as the electrophilic activator of the anomeric carbon and the resulting dibutylboron derivative of trichloroacetamide should not participate in any reaction with the acceptor hydroxyl and compete with the desired glycosylation. The positive charge on the anomeric carbon is counterbalanced by the non nucleophilic triflic anion. Glycosylation is completed via deprotonation with the triflic anion, as depicted in Scheme 1.



Scheme 1. Plausible mechanism of DBBOTf catalytic reaction



Scheme 2. DBBOTf promoted polymer-supported synthesis



Scheme 3. DBBOTf promoted solution mannosylation

To test these ideas we probed dibutylboron triflate as a promoter of glycosylation of MPEG-DOX-OH **1** with trichloroacetimidate **2**.[7] The reaction indeed took place at -45 °C giving **3**[8] in 95% yield[9] (Scheme 2). The glycosylation of MPEG-DOX-hexose **4** with disaccharide trichloroacetimidate **5** gave the desired trisacharide **6**[10] in 85% yield.

Reaction temperatures below -45 °C led to precipitation of the polymer; in the absence of MPEG glycosylations proceeded smoothly at temperatures as low as -78 °C. Examples of the latter reactions are mannosylations[11] of hydroxyls in phenylthio 2-deoxy-2-phthalimidoglucopyranosides **7** - **9**[12] with trichloroacetimidate **10** (Scheme 3) giving **11**,[13] **12**,[14] and **13**[15] in better than 50% yields. The compatibility of the promoter with the thio glycoside protection of the anomeric centre is a welcome finding allowing a subsequent use of this thioglucoside as glycosylation agent. The *trans*-anomeric specificity was excellent, and acetyl migration[16,3] to accepting hydroxyls was negligible. Since the reaction is fast at low temperatures (-78 °C), side reactions are minimized. In conclusion, DBBOTf is an efficient promoter of glycosylations with trichloroacetimidates, including the polymer-supported ones.

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7. *General procedure*: To the mixture of a donor (3 eq.), an MPEG-DOX-bound acceptor (1.0 eq.), and dry molecular sieves 4A in dry CH_2Cl_2 cooled to -45 °C was added 1M solution in CH_2Cl_2 of dibutylboron triflate (0.1 eq.; Aldrich) under argon. To quench the reaction after 30 minutes of continued stirring at -45 °C, solid $NaHCO_3$ was added, the mixture was stirred for 10 minutes, and the solids were filtered off through a celite bed. The product was obtained by precipitation with *t*-butylmethyl ether, or by filtration chromatography on a silica gel column (hexane-ethyl acetate combinations eluted all reaction components not linked to MPEG; MPEG-bound products were usually removed from the column with $CHCl_3$-25%MeOH; sometimes, however, both groups of substances co-eluted).

8. ^1H NMR ($CHCl_3$; δ; selected resonances): 5.13 (d, $J_{1,2}$=8.4 Hz, 1H, H-1); 5.12 (dd, $J_{3,4}$=9.0 Hz, $J_{4,5}$=10.0 Hz, 1H, H-4); 4.42 (dd, $J_{3,4}$=9.0 Hz, $J_{2,3}$=10.7, 1H, H-3); 4.30 (dd, $J_{1,2}$=8.4 Hz, $J_{2,3}$=10.7 Hz, 1H, H-2); 3.38 (s, 3H, $OC\underline{H}_3$); 1.94 (s, 3H, $OCOC\underline{H}_3$).

9. This is the isolated yield (by weight) of the glycosylated polymer showing in the ^1H NMR spectrum the same intensity of methyl signals of the acetyl group (at δ=1.94ppm) and the terminal methyl group of methylether polyethylene glycol (at δ=3.38ppm).

10. ^1H NMR ($CHCl_3$; δ; selected resonances): 5.35 (d, $J_{1,2}$=1.8 Hz, 1H, H-1c); 5.25 (d, $J_{1,2}$=8.2 Hz, 1H, H-1a); 4.92 (d, $J_{1,2}$=8.4 Hz, 1H, H-1b); 3.38 (s, 3H, $OC\underline{H}_3$); 2.03 (s, 3H, $OCOC\underline{H}_3$).

11. *General procedure*: To the mixture of a donor (1.25-1.50 eq.), an acceptor (1.0 eq.), and dry molecular sieves 4A in dry CH_2Cl_2 cooled to -45 °C was added 1M solution in CH_2Cl_2 of dibutylboron triflate (0.1 eq.; Aldrich) under argon. To quench the reaction after 30 minutes of continued stirring at -78 °C, solid $NaHCO_3$ was added, the mixture was stirred for 10 minutes, and the solids were filtered off through a celite bed. The filtrate was evaporated to dryness and further purified by chromatography on a silica gel column in hexane-ethyl acetate mixtures.

12. Synthetic procedures for these intermediates will be reported elsewhere.

13. ^1H NMR ($CHCl_3$; δ; selected resonances): 5.49 (d, $J_{1,2}$=10.5 Hz, 1H, H-1a); 5.40 (dd, $J_{1,2}$=2.0 Hz, $J_{2,3}$=3.1 Hz, 1H, H-2b); 4.94 (d, $J_{1,2}$=2.0 Hz, 1H, H-1b); 4.37 (dd, $J_{3,4}$=8.6 Hz, $J_{2,3}$=8.7, 1H, H-3a); 2.18 (s, 3H, $OCOC\underline{H}_3$).

14. ^1H NMR ($CHCl_3$; δ; selected resonances): 5.48 (d, $J_{1,2}$=10.5 Hz, 1H, H-1a); 5.35 (d, $J_{1,2}$=1.8 Hz, 1H, H-1b); 4.43 (dd, $J_{3,4}$=9.8 Hz, $J_{2,3}$=10.2, 1H, H-3a); 2.02 (s, 3H, $OCOC\underline{H}_3$).

15. ^1H NMR ($CHCl_3$; δ; selected resonances): 5.72 (d, $J_{1,2}$=10.5 Hz, 1H, H-1a); 5.61 (s, 1H, $PhC\underline{H}O_2$); 5.24 (d, $J_{1,2}$=1.7 Hz, 1H, H-1b); 4.71 (dd, $J_{3,4}$=8.8 Hz, $J_{2,3}$=10.6, 1H, H-3a); 2.00 (s, 3H, $OCOC\underline{H}_3$).

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