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1-Fluoropyridinium triflates: versatile reagents for transformation of thioglycoside into *O*-glycoside, glycosyl azide and sulfoxide

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Abstract—1-Fluoropyridinium triflates are versatile reagents to transform thioglycoside into *O*-glycoside, glycosyl azide and sulfoxide. The electronic nature of the substituents on the pyridine ring can control their ability to activate thioglycosides.

Biological activities of complex glycoconjugates drive chemist to develop efficient methods for the assembly of oligosaccharides as drug candidates or chemical probes.[1] For chemical synthesis of oligosaccharides, thioglycosides are the most versatile glycosyl donors in terms of stability towards chemical manipulations and high reactivity to the glycosylation. In order to transform thioglycosides into *O*-glycosides, a lot of thiophilic electrophiles have been developed, i.e. methyl triflate (MeOTf),[2] iodonium di-*sym*-collidine perchlorate (IDCP),[3] dimethyl(methylthio)sulfonium triflate (DMTST),[4] methyl- or phenylsulfenyl triflate (MeSOTf[5a] or PhSOTf[5b]), *N*-iodosuccinimide-triflic acid (NIS-TfOH),[6] Selectfluor™-$BF_3{\cdot}OEt_2$[7] and some others.[8] However, most of them require either their preparation beforehand, or mixing more than two reagents to prepare active species in situ. For simple operation, there is still a need to search an alternative promoter to be able to activate thioglycosides without any additive including Lewis or Brönsted acid. We report here new efficient method for the transformation of thioglycoside into *O*-glycoside, glycosyl azide and sulfoxide using commercially available 1-fluoropyridinium triflates **1** and **2** (Fig. 1).

1-Fluoropyridinium triflates were synthesized by Umemoto et al.[9] and some of them are commercially available. They are composed of an electrophilic fluorine atom attached to a pyridine ring and a triflate counteranion, which are utilized for fluorination of aromatics, alkenes,[10] sulfides[11] and hydrolysis of dithioacetals.[12] Their thiophilic property encouraged us to employ them as a promoter for transformation of thioglycosides into *O*-glycosides.[7] Their fluorinating ability increases as the electron density of the positive nitrogen sites decreases[10] and should be in proportion to ability to activate thioglycosides. We chose electron-rich 1-fluoro-2,4,6-trimethylpyridinium triflate (FTMPT; **1**) as a less reactive promoter and electron-poor 1-fluoro-2,6-dichloropyridinium triflate (FDCPT; **2**) as a more reactive one (Fig. 1). They would generate 2,6-disubstituted pyridine during the glycosylation and their sterically hindered nitrogen atom would not attack on oxocarbenium ion derived from thioglycoside.

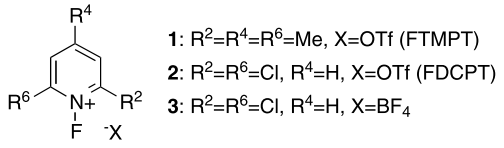

Figure 1.

The results of glycosylation of glycosyl acceptors **6–12** with glycosyl donors **4** and **5** using 1-fluoropyridinium triflates **1** and **2** are summarized in Table 1.[13] Electron-rich FTMPT **1** could activate reactive *O*-benzylated (armed) thioglycoside **4** by itself to give disaccharides **13–16** and **18** in good yields (entries 1–5). This method was compatible with acid-labile *p*-methoxybenzyl group, *tert*-butyldimethylsilyl group and allyl group having an olefin (entries 3–5). As expected from structural similarity to IDCP,[3] **1** turned out to be a less reactive promoter, which required room temperatures,

Keywords: 1-fluoropyridinium triflate; thioglycoside; *O*-glycoside; glycosyl azide; glycosyl sulfoxide.

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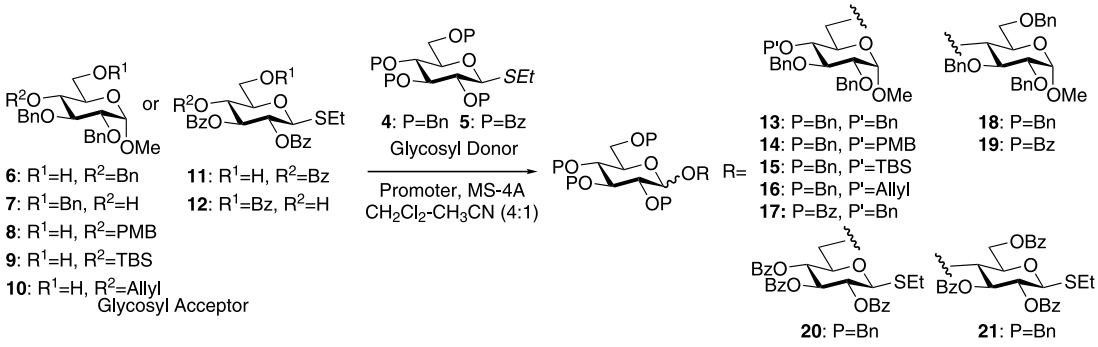
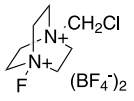
Table 1.



Entry	Promoter	Donor	Acceptor	Product	Condition[a]	Yield (%)	α:β[b]
1	**1**	**4**	**6**	**13**	A	86	35:65
2	**1**	**4**	**7**	**18**	A	79	54:46
3	**1**	**4**	**8**	**14**	A	76	34:66
4	**1**	**4**	**9**	**15**	A	96	45:55
5	**1**	**4**	**10**	**16**	A	87	43:57
6	**1**	**5**	**7**	**17**	A	0	-
7	**1**	**4**	**11**	**20**	A	70	43:57
8	**1**	**4**	**12**	**21**	A	92	80:20
9	**2**	**4**	**6**	**13**	B	72	6:94
10	**2**	**4**	**7**	**18**	B	78	36:64
11	**2**	**5**	**6**	**17**	C	78	β
12	**2**	**5**	**7**	**19**	C	73	β
13	**3**	**5**	**7**	**19**	C	77	β
14	Selectfluor	**5**	**7**	**19**	C	0[c]	-



Selectfluor

a) A: Donor (1.5 eq.), Promoter (2.1 eq.), rt, 12 h; B: Donor (1.3 eq.), Promoter (1.8 eq.), -40 °C, 1 h; C: Donor (1.3 eq.), Promoter (1.8 eq.), 0 °C, 1 h; b) The α/β ratios were determined by HPLC analysis; c) When $BF_3{\cdot}OEt_2$ was used with Selectfluor™, **19** was obtained in 59% yield.

12 h of reaction time and could not activate a less reactive *O*-benzoylated (disarmed) thioglycoside **5** (entry 6). Based on the difference of reactivity of thioglycosides, **1** could promote chemoselective glycosylation of disarmed thioglycoside acceptors **11** and **12** having a free hydroxyl at C-6 or C-4 with the armed thioglycoside donor **4** to give disaccharides **20** and **21** in 70 and 92% yield, respectively (entries 7 and 8).

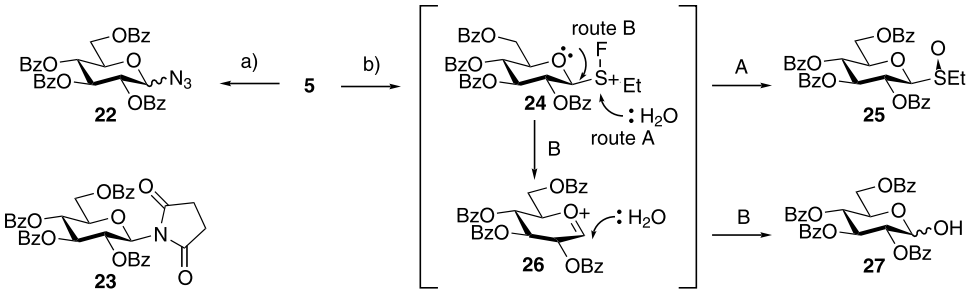
Instead of **1**, electron-poor FDCPT **2** was used for the glycosylation of **6** and **7** (entries 9–12). FDCPT **2** with higher fluorinating ability could activate not only the armed thioglycoside **4**, but also the disarmed **5** to give disaccharides **13**, **17**, **18** and **19** in good yields with predominant β-selectivity (entries 9–12). The higher β-selectivity for **4** without neighboring-group participation would result from lower reaction temperature required for **2** in acetonitrile[14] as co-solvent (entries 1 and 2 versus 9 and 10).[15]

In order to examine the effect of counteranion of 1-fluoropyridinium salts, tetrafluoroborate derivative **3** was used for the glycosylation of **7** with **5** to give **19** as efficiently as triflate derivative **2** (entry 13). It is noteworthy that Selectfluor™, a fluorinating reagent having the same tetrafluoroborate anion gave no glycosylated product without $BF_3{\cdot}OEt_2$ (entry 14).[7] In the latter case, nucleophilic tertiary amine generated from Selectfluor™ may disturb the glycosylation process.

Finally, some other nucleophiles were examined for the transformation of **5** (Scheme 1). When trimethylsilylazide was utilized as nucleophile, **2** could transform **5** into glycosyl azide **22β** along with a minor α-product **22α**,[16] which can be useful for the synthesis of *N*-linked glycopeptide. The use of NIS-TfOH instead of **2** gave not **22** but succinimide derivative **23**.[17]

When water was utilized as co-solvent, **2** oxidized **5** to give glycosyl sulfoxide **25** in excellent yield as well as Selectfluor.[18] This result means attack of an excess of water on the fluorosulfonium cation intermediate **24** would be faster than the formation of oxocarbenium ion **26**. In the glycosylation of alcohol, 1-hydroxy derivative **27** was obtained as a minor by-product due to slower attack of the least amount of water on **24** than the formation of **26**. Furthermore, it is noteworthy that this method was not accompanied by overoxidation to the corresponding sulfone observed in the oxidation using *m*-chloroperoxybenzoic acid even when an excess of **2** was used.

Thus, we have succeeded in transformation of thioglycosides into *O*-glycosides, glycosyl azide and sulfoxide using 1-fluoropyridinium triflates **1** and **2**. These promoters are commercially available and work well without any additive. Further studies on solid-phase synthesis of oligosaccharides using combination of thioglycosides and 1-fluoropyridinium triflates are underway in our laboratory.



Scheme 1. *Reagents and conditions*: (a) **2** (1.5 equiv.), $TMSN_3$ (6 equiv.), CH_2Cl_2–CH_3CN (4:1), 0°C, 1 h, **22**, 77% (α:β = 10:90); (b) **2** (2.0 equiv.), CH_3CN–H_2O (9:1), 0°C, 1 h, **25**, 91% (2:1 mixture).

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13. Spectra data of **13**, **17**–**21**, **22β** and **25** are consistent with the ones in the following reports. See: (a) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279; (b) Jona, H.; Mandai, H.; Chavasiri, W.; Takeuchi, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291–309; (c) Geurtsen, R.; Holmes, D. S.; Boons, G.-J. *J. Org. Chem.* **1997**, *62*, 8145–8154; (d) Li, C.; Arasappan, A.; Fuchs, P. L. *Tetrahedron Lett.* **1993**, *34*, 3535–3538; (e) Misbahi, K.; Lardic, M.; Ferriéres, V.; Noiret, N.; Kerbal, A.; Plusquellec, D. *Tetrahedron: Asymmetry* **2001**, *12*, 2389–2393.
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15. Acetonitrile as the sole solvent could not improve the β-selectivity of the glycosides. Furthermore, ether as a solvent known to be suitable for the α-selective glycosylation caused longer reaction time and poor yields due to low solubility of 1-fluoropyridinium triflates in ether.
16. Spectra data of new compound **22α**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09–7.85 (m, 8H), 7.60–7.27 (m, 12H), 6.10 (dd, 1H, J = 10.0, 9.9 Hz), 5.92 (d, 1H, J = 4.4 Hz), 5.71 (dd, 1H, J = 9.9, 9.6 Hz), 5.39 (dd, 1H, J = 4.4, 10.0 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.3, 165.8, 165.7, 165.3, 133.8, 133.6, 133.4, 133.3, 130.1, 130.0, 129.9, 129.8, 129.6, 129.0, 128.7, 128.6, 128.54, 128.51, 128.4, 86.5, 71.1, 70.1, 69.9, 68.8, 62.6; IR (neat): ν_{max} (cm^{-1}) 2958, 2925, 2115, 1721, 1245, 1088, 1069, 1025, 704, 685; FAB-MS m/z 622 $(M+H)^+$.
17. There are only a few reports on the transformation of thioglycosides into the corresponding glycosyl azide. See: (a) Matsuo, I.; Isomura, M.; Walton, R.; Ajisaka, K. *Tetrahedron Lett.* **1996**, *37*, 8795–8798; (b) Kerékgyártó, J.; Ágoston, K.; Batta, G.; Kamerling, J. P.; Vliegenthart, J. F. G. *Tetrahedron Lett.* **1998**, *39*, 7189–7192.
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