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Ready Transformation of Partially Unprotected Thioglycosides into Glycosyl Fluorides Mediated by NIS/HF–Pyridine or $Et_3N{\cdot}3HF$

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Dedicated to Prof. Benito Alcaide on the occasion of his 60th birthday

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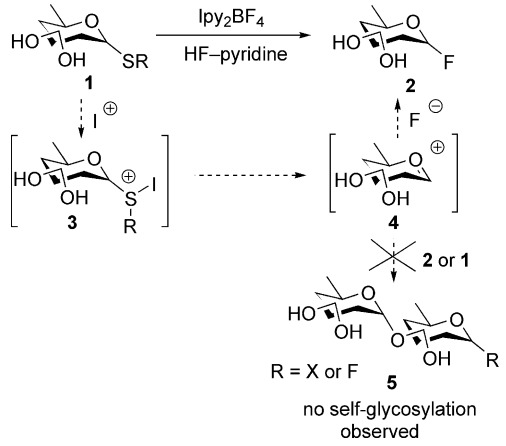
The transformation of partially unprotected phenyl 1-thioglycosides into glycosyl fluorides can be conveniently carried out by treatment with NIS in the presence of HF–pyridine. Other sources of halonium ions such as NBS, IDCP, have also been employed. The combination NIS/$Et_3N{\cdot}3HF$, where triethylamine–tris(hydrogen fluoride) ($Et_3N{\cdot}3HF$) replaces HF–pyridine, can also effect this transformation when acid-sensitive substituents are present.

Introduction

Glycosyl coupling, the key event in saccharide synthesis, requires the controlled assembly of a donor with an acceptor.[1] Traditionally, glycosylation strategies demand that all hydroxy groups of the donor must be protected, while the glycosyl acceptor normally has only one hydroxy group free.[2] As a consequence, the synthesis of biologically relevant oligosaccharides[3] incorporates a considerable number of protection-deprotection steps, thence resulting in lengthy processes. Minimization in the number of protection-deprotection steps in a glycosylation strategy has been accomplished by the use, among others, of rationally designed protecting groups[4] or by regioselective coupling of polyol glycosyl acceptors.[5] In this context, we have evaluated the influence of the O-2 substituent of the glycosyl donor in regioselective glycosylations.[6] We and others, have also explored the possibility of effecting glycosyl couplings where both partners could be partially unprotected.[7,8] Along this line, we believe that the development of methods that allow the direct exchange of anomeric leaving groups between partially unprotected glycosyl donors – or acceptors – would be useful, since it will avoid additional steps.[9]

We have described the use of bis(pyridine)iodonium(I) tetrafluoroborate[10] (IPy_2BF_4) for the conversion of thioglycosides[11] and *n*-pentenyl glycosides[12] into their semi-orthogonal[13,14] glycosyl fluoride partners.[15,16] In this transformation, IPy_2BF_4 functioned as a synthetic equivalent of iodine monofluoride,[17] thus being a source of electrophilic iodonium ion, which activates the anomeric leaving group (e.g. **1** → **3**, Scheme 1), and nucleophilic fluoride that reacts with the anomeric oxocarbenium ion (e.g. **4** → **2**, Scheme 1). However, our recently reported transformation of partially unprotected thioglycosides into glycosyl fluorides[18] (e.g. **1** → **2**, Scheme 1) had demanded the combination of IPy_2BF_4 with HF–pyridine,[19,20] the latter functioning as an additional source of nucleophilic fluoride anion intended to avoid self-glycosyl coupling of the intermediate oxocarbenium ion (e.g. **4** → **5**, Scheme 1).



Scheme 1. Transformation of partially unprotected thioglycosides into glycosyl fluorides.

Even though IPy_2BF_4 and HF–pyridine are commercially available reagents, we have sought for more accessible alternatives, and in this communication we disclose that *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), or bis-

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(collidine)iodonium perchlorate (IDCP),[21] can also be employed as halonium sources, whereas triethylamine–tris(hydrogen fluoride) ($Et_3N{\cdot}3HF$)[22] can replace HF–pyridine in the transformation of partially unprotected thioglycosides **1** into glycosyl fluorides **2**.[23]

Results and Discussion

For our study we selected phenyl 1-thioglycosides **6**–**13** as representative examples of polyol systems with different protecting groups, including acid-sensitive ones, and *n*-pentenyl glycoside **14**. Initially the thioglycosides were treated with the halonium source in the presence of HF–pyridine (20 equiv., unless otherwise noted) in CH_2Cl_2 at –40 °C. Compounds **6**–**9** (Table 1) embody examples of primary/secondary diols, where Ley's diacetal protecting group[24,25] imposes rigidity that helps to prevent a competing intramolecular glycosylation process with the 6-OH group, therefore minimizing the formation of undesired 1,5-anhydro derivatives. Eventually, glycosyl fluorides **15**–**17** were obtained in excellent yields upon treatment of compounds **6**–**8** with NIS/HF–pyridine (Table 1, Entries 1, 2, and 4).

Compound **9** furnished only a moderate yield of glycosyl fluoride **18** (Table 1, Entries 6–8), owing to the formation of substantial amounts of the 1,5-anhydro derivative. In this context, in the reaction of compound **10**, devoid of Ley's acetal protecting group, fluoride **19** was obtained in 37% yield (Entry 9), because of considerable intramolecular glycosylation leading to the 1,5-anhydro derivative. An attempt to thwart this undesired result by use of even 40 equiv. of HF–pyridine was unsuccessful (Entry 10).

Besides Ley's acetal groups, benzyl and acyl groups were also compatible with the reaction conditions (Table 1, Entries 4, 5, 9–12). The reaction of benzylidene derivative **12** with NIS/HF–pyridine gave variable amounts of glycosyl fluoride **21** (ca. 45%) (Table 1, Entry 14), the observed by-products resulting from loss of the benzylidene protecting group.

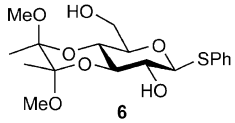
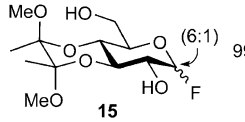
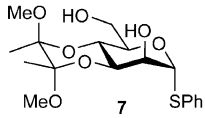
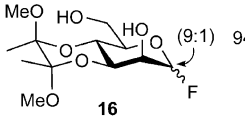
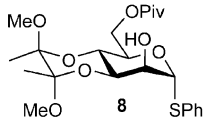
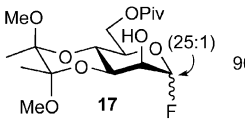
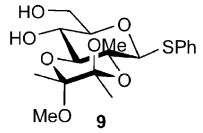
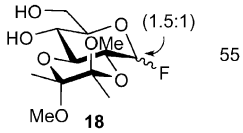
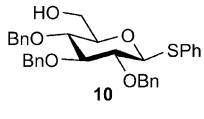
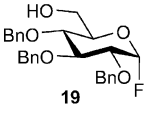
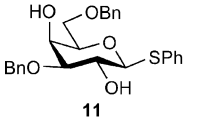
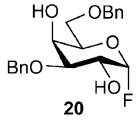
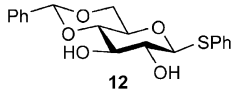
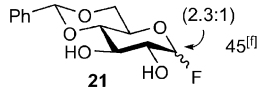
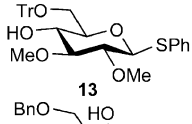
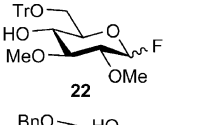
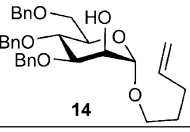
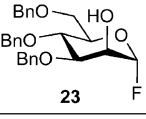
Compound **13**, with an acid-labile trityl protecting group, did not yield the desired glycosyl fluoride **22** but a complex mixture, which was not analyzed (Table 1, Entry 15).

The use of NBS as the halonium source was also examined, and normally resulted in reduced yields of glycosyl fluorides (compare Entries 2 with 3, and 4 with 5, and 11 with 12). Bis(collidine)iodonium perchlorate (IDCP) in the presence of HF–pyridine was also successful in promoting the fluorination of thioglycoside **9** (Entry 8). The use of iodine in the presence of HF–pyridine did not cause any transformation in compound **11**, even at room temperature.[26]

The observed anomeric α/β ratios varied with the halonium source employed.[27,28] On the other hand, the reaction of *n*-pentenyl glycoside **14** with IDCP in the presence of HF–pyridine furnished only limited amounts of glycosyl fluoride **23**, a major side reaction being the IF addition across the terminal double bond.[12b]

In order to extend the applicability of this procedure to thioglycosides with acid-sensitive functionalities, we turned our attention to $Et_3N{\cdot}3HF$. This reagent, non-corrosive in

Table 1. Preparation of glycosyl fluorides from thioglycosides, by reaction with a halonium source (NIS and NBS: 1.2 equiv.; IDCP: 2.5 equiv.) in the presence of HF–pyridine in CH_2Cl_2 at –40 °C.

Entry	Starting material	Reagent HF–pyridine (equiv.)[a]	Glycosyl fluoride (α/β) ratio[b]	Yield (%)
1	 **6**	NIS	 (6:1) **15**	99
2	 **7**	NIS	 (9:1) **16**	94
3	**7**	NBS	**16** (7:1)	80
4	 **8**	NIS	 (25:1) **17**	90
5	**8**	NBS	**17** (a only)	83
6	 **9**	NIS	 (1.5:1) **18**	55
7	**9**	NBS	**18** (2.5:1)	55
8	**9**	IDCP	**18** (1.7:1)	70
9	 **10**	NIS	 **19**	37[c]
10	**10**	NIS (40)	**19**	40[d]
11	 **11**	NIS	 **20**	99
12	**11**	NBS	**20** (a only)	62
13	**11**	iodine	**20**	–[e]
14	 **12**	NIS	 (2.3:1) **21**	45[f]
15	 **13**	NIS	 **22**	–[g]
16	 **14**	IDCP (10)	 **23**	42[h]

[a] Unless otherwise noted, 20 equiv. were used throughout. [b] The anomeric (α/β) ratio was determined from the integration of the anomeric signals in the ^1H NMR spectra of the crude reaction mixture. [c] 1,5-Anhydro derivative (58% yield) was also isolated. [d] 1,5-Anhydro derivative (52% yield) was also isolated. [e] No reaction was observed, even at room temp. [f] The yield for this transformation was erratic, and compounds resulting from the deprotection of the benzylidene ring were normally observed. [g] A complex reaction mixture was obtained under different reaction conditions. [h] Compounds resulting from addition of IF across the double bond were also observed (14%).

borosilicate glassware, has been used as a source of fluoride ion and was selected because of its almost neutral pH.[22] Accordingly, our results for the transformation of thioglycosides into glycosyl fluorides by means of NIS/Et_3N·3HF are outlined in Table 2. The thioglycosides were treated with NIS (2.0 equiv.) in the presence of Et_3N·3HF in CH_2Cl_2 at –20 °C. These transformations required, in general, higher temperatures and longer reaction times to proceed, probably due to the limited activation of the NIS by Et_3N·3HF when compared with the more acidic HF–pyridine. Thioglycosides **6**, **7**, and **11**, which had given excellent yields of glycosyl fluorides with NIS/HF–pyridine (Table 1, Entries 1, 2, 11) also furnished excellent yields with NIS/Et_3N·3HF (Table 2, Entries 1, 2, 4). Benzylidene derivative **12** did not give any noticeable amount of fluoride **21** (Table 2, Entry 5). On the contrary, trityl derivative **13**, which had not endured the treatment with HF–pyridine, gave acceptable yields of glycosyl fluoride **22** (Table 2, Entries 6, 7).

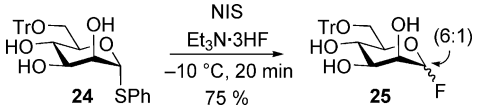
Table 2. Preparation of glycosyl fluorides from thioglycosides by reaction with NIS (2 equiv.) in the presence of Et_3N·3HF in CH_2Cl_2.

Entry[a]	Starting material	Temp. [°C]	Reaction time [min]/ Et_3N·3HF [equiv.]	Glycosyl fluoride[c]	Yield [%]
1	**6**	–20	60/40	**15**	97
2	**7**	–20	40/40	**16**	95
3	**9**	–20 to r.t.	480/120	**18**	37[a]
4	**11**	–20	5/40	**20**	93
5	**12**	–10	120/40	**21**	–[b]
6	**13**	0 to r.t.	180/40	**22**	57[c]
7	**13**	r.t.	180/120	**22**	67[d]

[a] Unreacted thioglycoside **9** (58%) was also isolated. [b] No appreciable amount of glycosyl fluoride **21** was observed after 2 h. [c] Unreacted thioglycoside **13** (32%) was also observed (^{1}H NMR). [d] Unreacted thioglycoside **13** (22%) was also observed (^{1}H NMR).

Conformationally disarmed[24b,29] glycosyl fluorides **9** and **12** did not react readily with NIS/Et_3N·3HF (Table 2, Entries 3, 5), thus illustrating that this reagent system is a less potent source of iodonium ion than NIS/HF–pyridine.

Finally, trityl-protected triol **24** was easily transformed into glycosyl fluoride **25**, as an α/β (6:1) mixture, in 75% yield (Scheme 2).



Scheme 2. Transformation of triol **24** into glycosyl fluorides α/β-**25**.

The anomeric (α/β) ratio of the glycosyl fluorides was determined, throughout this work, from the integration of its anomeric signals in the ^{1}H NMR spectra of the crude reaction mixture. The assignment of the α- or β-orientation of the glycosyl fluorides was based on NMR spectroscopic data. Thus, α-anomers, in the D-gluco (**15**, **18**) and D-manno (**16**, **17**, **25**) series, displayed ^{1}H NMR (300 MHz, $CDCl_3$) chemical shifts within the range δ = 5.63–5.51 ppm, whereas those of the corresponding β-anomers appeared between δ = 5.37 and 5.12 ppm.[30] These values were in agreement with those found for the $^1J_{C,H}$ coupling constants of the anomeric carbon atoms of α-**25** (δ = 5.51 ppm) and β-**25** (δ = 5.32 ppm), 181.8 and 168.0 Hz, respectively.[31]

Conclusions

Partially unprotected phenyl 1-thioglycosides can be transformed into glycosyl fluorides. Primary hydroxy groups can be present if 3,4-*O* Ley's-type diacetal groups are in the molecule, whereas the method is completely tolerant with secondary OH groups. The method involves treatment of the thioglycoside with a halonium ion source in the presence of either HF–pyridine or Et_3N·3HF. Within the sources for halonium ion examined, IDCP and NIS gave better results than NBS, whereas iodine did not promote any transformation. The combination NIS/HF–pyridine is more potent in provoking the reaction of thioglycosides, while NIS/Et_3N·3HF is more tolerant of acid-sensitive functionalities. This method represents a more economic alternative to IPy_2BF_4/HF–pyridine, recently described to effect this transformation.[18]

Experimental Section

General: Starting *n*-pentenyl glycoside and thioglycosides were prepared according to described procedures. The glycosyl fluorides reported in this paper have been described previously[18] with the exception of compounds **17** and **25**. ^{1}H and ^{13}C NMR spectra were recorded with either Varian Inova-300 or Inova-400 spectrometers. NMR spectra were recorded in $CDCl_3$ solutions with the residual solvent signal as internal reference. Mass spectra were recorded with an HP 1100 spectrometer by using the electrospray (ES) chemical ionization method in its positive mode. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Elemental analyses were carried out with a Carlo Erba EA1108 apparatus. Flash column chromatography was performed on 230–400 mesh silica gel. Thin-layer chromatography was conducted on Kieselgel 60 F254 (Merck). Spots were first observed under UV irradiation (254 nm) and then by charring with a solution of aqueous H_2SO_4 (20%, 200 mL) in AcOH (800 mL).

General Procedure for the NIS/HF–Pyridine-Mediated Transformation of Thioglycosides into Glycosyl Fluorides: To a solution of *N*-iodosuccinimide (1.2 equiv.) in dry CH_2Cl_2 under argon cooled to –40 °C was added HF–pyridine (20 equiv.) followed by a solution of the thioglycoside in dry CH_2Cl_2. After all the starting material had disappeared (TLC), the reaction mixture was quenched with pyridine and washed with 10% aqueous sodium thiosulfate containing sodium hydrogen carbonate, and water. The organic layer was dried, concentrated, and the residue purified by flash chromatography.

General Procedure for the NIS/Et_3N·3HF-Mediated Transformation of Thioglycosides into Glycosyl Fluorides: To a solution of the thioglycoside in dry CH_2Cl_2 under argon cooled to –20 °C was added *N*-iodosuccinimide (2.0 equiv.) followed by Et_3N·3HF. After the starting material had disappeared (TLC), the reaction mixture was

quenched with Et_3N and washed with 10% aqueous sodium thiosulfate containing sodium hydrogen carbonate, and water. The organic layer was dried, concentrated, and the residue purified by flash chromatography.

Selected Data for 6-*O*-Pivaloyl-3-*O*,4-*O*-[(2′*S*,3′*S*)-2′,3′-dimethoxybutan-2′,3′-diyl]-α-D-glucopyranosyl Fluoride (α-17): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.52 (dd, J = 49.0, 1.3 Hz, 1 H), 4.55 (dd, J = 12.1, 1.9 Hz, 1 H), 4.28–3.96 (m, 5 H), 3.26 (s, 3 H), 3.23 (s, 3 H), 1.31 (s, 3 H), 1.27 (s, 3 H), 1.19 (s, 9 H) ppm. API-ES (positive) MS: m/z = 398.5 $[M + NH_4]^+$, 403.3 $[M + Na]^+$. $C_{17}H_{29}FO_8$ (380.18): calcd. C 53.67, H 7.68; found C 53.43, H 7.56.

Reaction of Phenyl 6-*O*-Trityl-1-thio-⟨-D-mannopyranose (24) with NIS/Et_3N·3HF: To a solution of the thioglycoside **24** (52 mg, 0.1 mmol) in dry CH_2Cl_2 (5 mL) under argon cooled to –10 °C was added *N*-iodosuccinimide (44.8 mg, 0.2 mmol, 2.0 equiv.) followed by Et_3N·3HF (0.326 mL, 2 mmol). After the starting material had disappeared (20 min), the reaction mixture was quenched with Et_3N and partially concentrated in the cold to remove most of the CH_2Cl_2. The resulting solution was then submitted to filtration through a short pad of silica gel (CH_2Cl_2/MeOH, 95:5), and the purified fractions were resubmitted to flash chromatography (EtOAc). Pure α-**25** (24 mg, 57%) was first eluted, followed by a mixture of α/β-**25** (8 mg, 18%). **α-25:** $[\alpha]_D$ = +9.9 (c = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.14 (m, 15 H), 5.51 (dd, J = 49.4, 1.3 Hz, 1 H), 3.96 (m, 1 H), 3.85–3.63 (m, 3 H), 3.38 (dd, J = 9.9, 3.8 Hz, 1 H), 3.33 (dd, J = 9.9, 4.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3 (×3), 128.5 (×6), 128.0 (×6), 127.3 (×3), 107.3 (d, J = 219.4 Hz), 87.4, 72.1 (d, J = 2.5 Hz), 70.6, 69.1, 68.7 (d, J = 38.4 Hz), 63.9 ppm. API-ES (positive) MS: m/z = 425.5 $[M + H]^+$, 447.7 $[M + Na]^+$. $C_{25}H_{25}FO_5$ (424.17): calcd. C 70.74, H 5.94; found C 70.65, H 5.68.

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