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A facile and convenient synthesis of disarmed glycosyl fluorides using in situ-generated iodine monofluoride (see Ref. 1)

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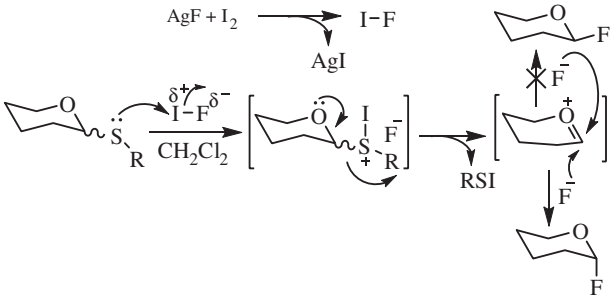
ABSTRACT

A facile and convenient synthesis of disarmed glycosyl fluorides using in situ-generated iodine monofluoride is reported. The method is tolerant to most of the popularly used protecting groups and gives exclusively the α-anomeric product in very good yields.

Glycosyl fluorides are versatile building blocks in the synthesis of oligosaccharides. Though known since 1923,[2] they gained importance only after their successful application as a glycosyl donor by Mukaiyama and co-workers using $SnCl_2$–$AgClO_4$ as the activator.[3] Subsequently a number of reaction conditions were developed for their activation with ease.[4] This, along with their relative stability, made them a favorable choice of many synthetic glycochemists in the years followed.

Glycosyl fluorides can be prepared by a number of methods. Sugars with a reducing end can be converted into the corresponding glycosyl fluorides using any of the reagent systems, namely, 2-fluoro-1-methylpyridinium tosylate,[5] diethyl-1,1,2,3,3,3-hexafluoropropylamine,[6] pyridinium poly(hydrogen fluoride),[7,8] DAST,[9,10] DEAD/PPh_3, and $Et_3O^+BF_4^-$,[11] *N*,*N*-diisopropyl(fluoro-2-methyl-1-propenyl)amine,[12] $CF_3ZnBr_2{\cdot}2CH_3CN$, and $TiCl_4$,[13] Selectfluor[14] and its analogs,[15] *N*,*N*-diethyl-α,α-difluoro-(*m*-methylbenzyl)amine,[16] *n*-$C_4F_9SO_2F$-$NR_3(HF)_3$-NR_3,[17] or 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride.[18] They can also be accessed from glycosyl acetates[7] and orthoesters[19] using pyridine·(HF)x, or HF-$MeNO_2$.[20,21] Glycosyl triazoles[22] and tetrazoles[23] can also be converted into the corresponding fluorides using (HF.pyridine). Alternatively, fluoride displacement of other glycosyl halides can be achieved using AgF,[24,25] $AgBF_4$,[26] $Et_3N.3HF$,[27] ZnF_2,[28] or $CF_3ZnBr_2{\cdot}2CH_3CN$.[13] Also, thioglycosides have been converted into their corresponding glycosyl fluorides using DAST/NBS,[29] 4-methyl(difluoroiodo) benzene,[30] selectfluor,[14] or $I(Py)_2BF_4$[31,32] as the reagent.

In the latter category of reactions, the fluoride donor reagents used are either corrosive, moisture sensitive, foul smelling, toxic, and/or expensive. A cheaper, easy-to-handle alternative that can serve the purpose under mild conditions must therefore be welcome. Thioglycoside-activation has been one of the versatile applications of iodine and its inter halogen compounds in carbohydrate chemistry. While armed thioglycosides can be easily activated by molecular iodine[33,34] for glycosylation with an acceptor, the disarmed thioglycosides require interhalogens[35] for the purpose; and this observation prompted us to investigate the possibility of converting the disarmed thioglycosides into the corresponding fluorides using iodine monofluoride (IF). IF has been previously reported for the conversion of glycals to 2-iodo glycosyl fluorides.[36] It can be conveniently generated in situ from molecular iodine, a cheap and easy-to-handle reagent and AgF (Scheme 1).[36]



Scheme 1. In situ-generation of I–F and its reaction with thioglycosides.

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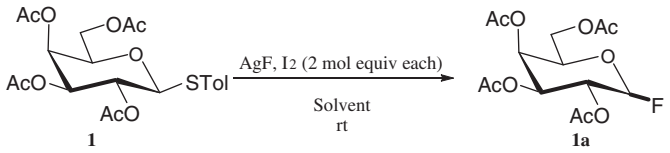
Table 1
Reaction of a disarmed thiogalactoside with AgF-I_2



1 1a

Solvent	Time (h)	Yield (%)[a]	**1a** (α:β)
MeCN	0.25	52	1:3
CH_2Cl_2	1.0	76	1:0
1,4-Dioxane	18	81	3:1

[a] Isolated yield.

An alternate method reported in the literature for the generation of IF involves the use of anhydrous liquid HF, an extremely corrosive reagent, in combination with N-bromosuccinimide and was not used in the current study. To examine the feasibility of the reaction tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**1**) was treated with a mixture of AgF and I_2 at room temperature in the dark. Based on the observations we have made earlier in the context of the I_2-promoted glycosylation reactions, the reaction was carried out in three different solvent systems and the results are summarized in Table 1.

As can be seen from Table 1, promising results were obtained in all the three cases. Thus, although the reaction was found to be faster in MeCN, the yield obtained in the case was inferior to those employing both CH_2Cl_2 as well as dioxane. In CH_2Cl_2 the reaction went to completion in 1 h with complete stereoselectivity giving the desired α-fluoride **1a-α** in good isolated yield. In the case of dioxane on the other hand the reaction was more effective (yield 81%) but required a longer time for completion. In the case of both MeCN as well as dioxane fluoride **1a** was obtained as a mixture of α- and β-anomers, though opposing stereoselectivity was observed in the two cases. As for the IF concentration, the use of less than 2 mol equiv of the reagents (each of AgF and I_2) led to inferior results (values not shown). Thus, for further studies 2 mol equiv of

Table 2
Reaction of various thioglycosides with AgF-I_2 system[a]

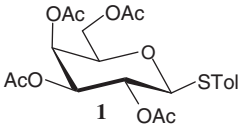
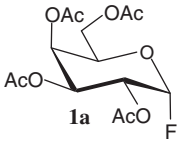
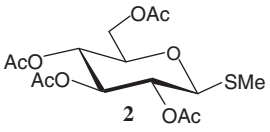
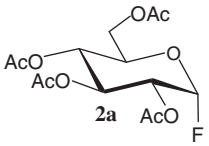
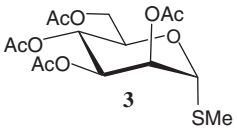
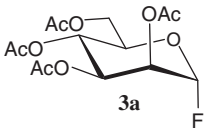
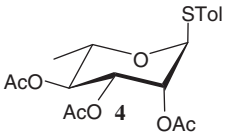
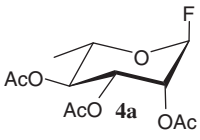
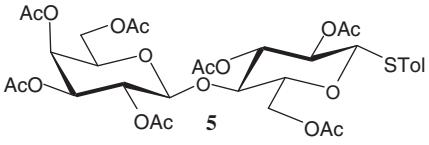
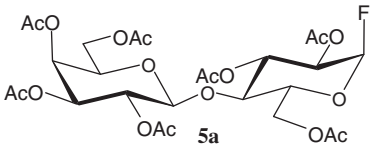
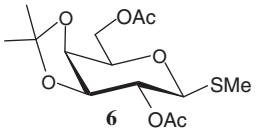
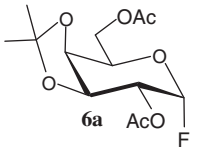
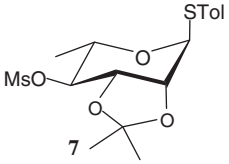
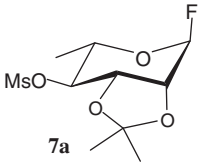
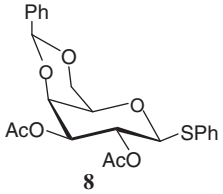
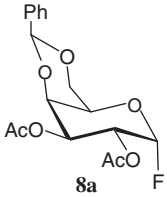
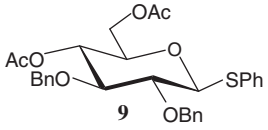
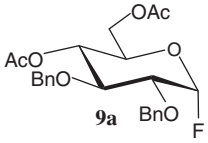
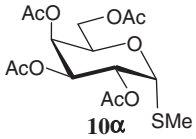
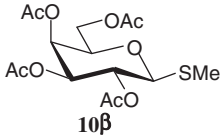
Starting material	Product	Isolated yield (%)	$[\alpha]_D$ at 20 °C c = 1 ($CHCl_3$)	
			Observed	Literature
 1	 1a	81	+97.4	+96.5[38]
 2	 2a	76	+89.20	+90.08[2]
 3	 3a	85	+24.0	+21.5[39]
 4	 4a	80	−27.0	−30.0[40]
 5	 5a	72	+42.3	+43.0[41]
 6	 6a	78	+108.0	—
 7	 7a	83	+46.2	—

Table 2 (*continued*)

Starting material	Product	Isolated yield (%)	$[\alpha]_D$ at 20 °C c = 1 ($CHCl_3$)	
			Observed	Literature
 **8**	 **8a**	67	+175.4	–
 **9**	 **9a**	59	−10.5	–
 **10α**	**1a**	>80	–	–
 **10β**	**1a**	>80	–	–
10 α/β	**1a**	>80	–	–

[a] Thioglycoside (1 mmol) was treated with AgF-I_2 (2 mmol each) in anhydrous CH_2Cl_2 at rt in the dark.

Table 3
Method-comparison with literature methods

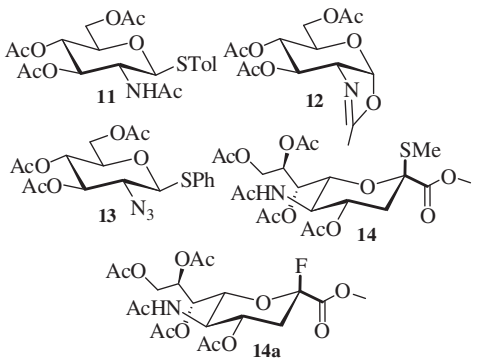
Substrate	Reaction condition		Yield (%)
	Reagent	Time, temp	
2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose	Py·$(HF)_n$[8]	10 h, rt	53 **2a**-α
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide	ZnF_2, 2,2′-bipyridine[28]	5.15 h, 82 °C	61 **2a**-β
Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside	4-Methyl (difluoroiodo) benzene[30]	Over-night −78 °C	65 (**2a**-α/β)
2	AgF, I_2 (current)	1 h, rt	76 (**2a**-α)

the fluorinating agent in CH_2Cl_2 at rt was chosen as optimum for the reaction.

In order to establish wider acceptability of the method, the reaction was extended to a range of thioglycoside-substrates. Thus, representative aryl and alkyl thioglycosides of various mono- (D-galactose, D-glucose, D-mannose and L-rhamnose) and disaccharides (lactose) bearing different protecting groups (acid-labile groups such as the isopropylidene and benzylidene acetals and the base-labile groups such as the acetate and mesylate) were studied[37] and the results are summarized in Table 2. It can be clearly seen from Table 2 that all the nine thioglycoside-substrates studied gave their respective α-glycosyl fluorides in good yield with complete functional group tolerance in all the cases. However, in the case of substrate **9** the yield was found to be only 59% owing to the partial cleave of the benzyl ether protection.

Interestingly, in separate experiments when the two anomeric thioglycosides **10α** or **10β**, either alone or as a mixture, was treated with the fluorinating agent, the α-fluoride **2a** was the only product obtained which was isolated in >80% yield. This clearly showed that the reaction occurred via the oxocarbenium ion intermediate following a path as shown in Scheme 1. In MeCN or dioxane on the other hand there could be participation by the solvent molecules and hence could lead to a mixture of isomeric fluorides as can be seen from Table 1. Use of these solvents in the stereoselective synthesis of 1,2-*cis*-oriented glycosides is well known in the literature.

When the glycosyl fluoride formation was attempted with *p*-tolyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (**11**), the formation of oxazoline **12**, not surprisingly though, was observed. The thioglycoside **13** that can serve as a precursor to the 2-acetamido-2-deoxy-glucopyranosyl analogues on the other hand, failed to react owing to the highly 'disarming' nature of the azido substituent on the C-2 position of the hexosyl unit. Likewise, the methylthiosialoside derivative **14** though was susceptible to the fluorinating agent, gave the expected sialosyl fluoride **14a** (δ_F −116 in the 19F NMR spectrum) only partially in spite of using excess IF (in situ) for prolonged durations of reaction.



A comparison of the current method with those reported in the literature for the synthesis of 2,3,4,6-tera-*O*-acetyl-D-glucopyranosyl fluoride as the example (where most comparison was possible) has been provided in Table 3. It is evident from Table 3 that the current method proves faster and high yielding among the methods compared. The method using Py.$(HF)_n$ not only required longer reaction time but also suffered from poorer yield.

The ZnF_2/2,2′-bipyridine-method required heating while the 4-methyl(difluoroiodo)benzene-method required cooling for the methods to be effective. Besides, it was also found that the latter reagent is not available commercially. The only limitation in the case of the current method noted was that the required stirring in the dark, which could be achieved easily by wrapping the flask with aluminum foil.

In conclusion, a facile and effective method for the conversion of various thioglycosides to their respective glycosyl fluorides using in situ-generated IF as the fluorinating agent has been developed with good functional group tolerance and isolated yields. The fluorides obtained were exclusively α-anomers in all the cases when the reaction was carried out in CH_2Cl_2. All thioglycosides except those bearing a nitrogen substituent on the C-2 position of the pyranosyl ring gave satisfactory yields.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.024.

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37. *Typical experimental procedure*: AgF (2 mmol) was added to a solution of the thioglycoside (1 mmol) in anhydrous CH_2Cl_2 in the dark followed by addition of iodine (2 mmol) at rt. After 60 min (when the reaction was found to be complete), the mixture was diluted with excess CH_2Cl_2 and was quenched by the addition of an ice-cold aqueous solution of $Na_2S_2O_7$ and was filtered through a Celite bed. The filtrate was washed with ice-cold aqueous solution of NaHCO3 in a separating funnel and after drying over Na_2SO_4, was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 200–430 mesh; eluent, EtOAc-*n*-hexane, 2:3 to 1:1 depending upon the substrate) to afford the corresponding glycosyl fluoride in pure form.
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42. *Physical data and NMR characterisation*:
(a) *2,6-Di-O-acetyl-3,4-O-isopropylidene-α-D-galactopyranosyl fluoride (**6a**)* Yield 78%; colorless solid; mp 82 °C; $[\alpha]_D$ +108 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (dd, $J_{1\text{-}F}$ = 53 Hz, $J_{1\text{-}2}$ = 2.8 Hz, 1H, H-1), 5.00 (ddd, $J_{2\text{-}F}$ = 23 Hz, $J_{2\text{-}1}$ = 2.8 Hz, $J_{2\text{-}3}$ = 7.4 Hz, 1H, H-2), 4.44–4.29 (2 × m, 5H, H-3, H-4, H-5, H-6a and H-6b), 2.15, 2.11 (2 × s, 6H, 2 × $-COCH_3$), 1.51, 1.35 (2 × s, 6H, $-C(CH_3)_2$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −151.47 (dd, $J_{1\text{-}F}$ = 53 Hz, $J_{2\text{-}F}$ = 23 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.79, 170.18, 110.53, 105.35, 103.09, 72.65, 70.13, 69.90, 68.36, 68.32, 63.24, 27.56, 26.11, 20.87, 20.81; IR (Neat) ν_{max} 2988, 1744, 1372, 1224, 1169, 1075, 1051, 926 cm^{-1}; HRMS: *m*/*z* calculated for $C_{13}H_{19}FNaO_7$: 329.1013. Found: 329.1030.
(b) *2,3-o-Isopropylidene-4-o-methanesulfonyl-α-L-rhamnopyranosyl fluoride (**7a**)* Yield 83%; pale yellow solid; mp 111 °C; $[\alpha]_D$ +46.2 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, $J_{1\text{-}F}$ = 48 Hz, 1H, H-1), 4.42–4.32 (m, 3H, H-2, 3 and 4), 3.96–3.92 (m, 1H, H-5), 3.19 (s, 3H, $-SO_2CH_3$), 1.58, 1.39 (2 × s, 6H, $-C(CH_3)_2$), 1.38 (d, $J_{5\text{-}6}$ = 5.8 Hz, 3H, $-CH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −133.08 (dd, $J_{1\text{-}F}$ = 48 Hz, $J_{2\text{-}F}$ = 3.7 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.90, 106.02, 103.90, 82.74, 75.30, 75.18, 74.71, 66.2, 39.14, 27.61, 26.24, 16.84; IR (Neat) ν_{max} 2990, 1357, 1224, 1177, 1085, 1001, 966 cm^{-1}; HRMS: *m*/*z* calculated for $C_{10}H_{17}FNaO_6S$: 307.0628. Found: 307.0645.
(c) *2,3-Di-O-acetyl-4,6-o-benzylidene-α-D-galactopyranosyl fluoride (**8a**)* Yield 68%; colorless solid; mp 82 °C; $[\alpha]_D$ +175.4 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H, Ar-H), 7.39–7.35 (m, 3H, Ar-H), 5.89 (dd, $J_{1\text{-}F}$ = 54 Hz, $J_{1\text{-}2}$ = 2.56, 1H, H-1), 5.53 (s, 1H, −CHPh), 5.43–5.31 (m, 2H, H-2 and H-3), 4.53 (d, $J_{4\text{-}3}$ = 2.9 Hz, 1H, H-4), 4.32 (dd, $J_{6a\text{–}6b}$ = 12.7 Hz, $J_{5\text{-}6}$ = 1.64 Hz, 1H, H-6a), 4.06 (dd, $J_{6a\text{-}6b}$ = 12.7 Hz, $J_{5\text{–}6}$ = 1.64 Hz, 1H, H-6b), 4.00 (br s, 1H, H-5), 2.11, 2.10 (2 × s, 6H, 2 × $-COCH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −149.63 (dd, $J_{1,F}$ = 54 Hz, $J_{2,F}$ = 22 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.55, 170.07, 137.22, 129.18, 128.25, 126.16, 106.36, 104.11, 100.90, 73.24, 68.62, 67.96, 67.51, 67.27, 64.44, 64.42, 20.89, 20.66; R (Neat) ν_{max} 2917, 2847, 1743, 1372, 1221, 1163, 1076, 1050, 1020, 991 cm^{-1}; HRMS: *m*/*z* calculated for $C_{17}H_{19}FNaO_7$: 377.1013. Found: 377.1018.
(d) *4,6-Di-O-acetyl-2,3-di-O-benzyl-α-D-glucopyranosyl fluoride* (**9a**).
43. Yield 59%; colorless syrup; $[\alpha]_D$ −10.5 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 10H, Ar-H), 5.51 (dd, $J_{1,F}$ = 52 Hz, $J_{1,2}$ = 2.64 Hz, 1H, H-1), 5.06 (pt, *J* = 9.8 Hz, 1H, H-4) 4.87, 4.66 (2 × d, *J* = 11.5 Hz, 2H, $-OCH_2Ph$), 4.80, 4.69 (2 = d, *J* = 11.8, 2H, $-OCH_2Ph$), 4.22 (dd, $J_{5,6}$ = 3.8 Hz, $J_{6a,6b}$ = 12.6 Hz, 1H, H-6a); 4.06–4.01 (m, 2H, H-5 and 6b), 3.93 (pt, *J* = 9.48 Hz, 1H, H-3), 3.61 (ddd, $J_{2,F}$ = 25 Hz, $J_{1,2}$ = 2.64 Hz, $J_{2,3}$ = 9.5 Hz, 1H, H-2), 2.06, 1.92 (2 × s, 6H, $-COCH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −150.07 (dd, $J_{1,F}$ = 52 Hz, $J_{2,F}$ = 25 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.61, 169.49, 138.09, 137.40, 128.61, 128.44, 128.19, 128.03, 128.85, 128.80, 127.85, 127.80, 106.34, 104.07, 79.21, 78.96, 78.45, 75.47, 73.71, 70.18, 68.60, 61.67; IR (Neat) ν_{max} 2915, 1745, 1365, 1237, 1114, 1043, 913 cm^{-1}; HRMS: *m*/*z* calculated for $C_{24}H_{27}FNaO_7$: 469.1639. Found: 469.1642.