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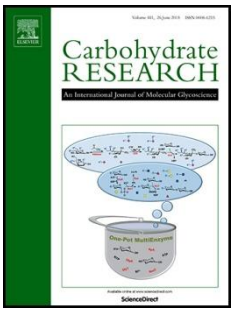

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Synthesis of glycosyl fluorides from (phenylthio)glycosides using IF_5-pyridine-HF

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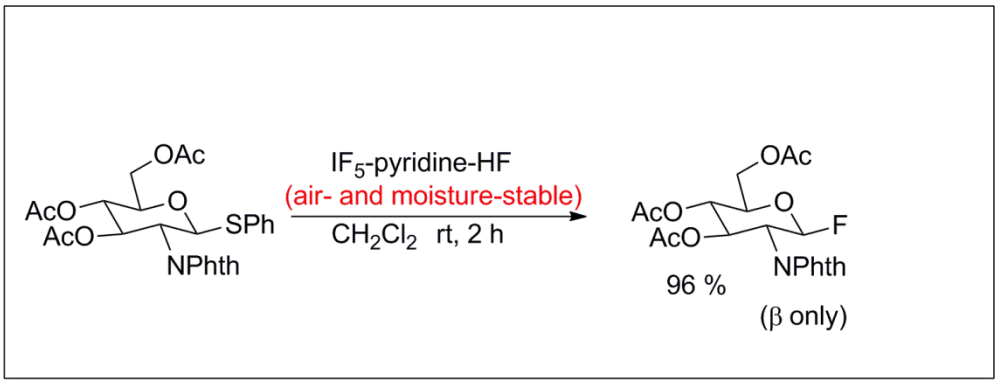
Highlights

Glycosyl fluorides were synthesized from (phenylthio)glycosides.> IF_5-pyridine-HF was used for the synthesis. > IF_5-pyridine-HF is air- and moisture stable, and easy to use. > Various kinds of glycosyl fluorides were synthesized.

Graphical Abstract



1g **2g**

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ABSTRACT

IF_5-pyridine-HF, an air- and moisture-stable fluorinating reagent, was applied to the synthesis of glycosyl fluorides from (phenylthio)glycosides. Common protecting groups of alcohol and diol can tolerate the reaction conditions performed, and therefore, the present method is applicable to the synthesis of various glycosyl fluorides.

keywords:

glycosyl fluorides

(phenylthio)glycosides

IF_5-pyridine-HF

air- and moisture-stable

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1. Introduction

Glycosyl fluorides have been successfully used as glycosyl donors in C-glycosydation and O-glycosylation, because of their exceptional stability and ease of handling compared to other halogen derivatives.[1-4] Glycosyl fluorides are also known to have considerable importance as substrates and inhibitors in enzymatic reactions,[5,6] and so their synthesis is becoming increasingly important.

Glycosyl fluorides were generally prepared from the corresponding thioglycosides by

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the reaction with fluorinating reagent such as IPy_2BF_4,[7,8] IF,[9,10] $ArIF_2$,[11] Xtalfluor,[12] amine-HF with NIS,[13] and most commonly DAST with an oxidant such as NBS.[14] However, DAST is moisture sensitive and thermally unstable,[15] and NBS can cause the formation of by-products.[16] Therefore, a safer and more reliable method for the synthesis of glycosyl fluorides is desired. Recently, we reported synthesis of a new fluorinating reagent, IF_5-pyridine-HF, and its application to fluorination reactions.[17,18] As IF_5-pyridine-HF is an air- and moisture-stable fluorinating reagent, we applied IF_5-pyridine-HF for the synthesis of glycosyl fluorides from (phenylthio)glycosides.

2. Results and discussion

The reaction of phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-1-thioglucopyranoside (**1a**) with IF_5-pyridine-HF was carried out in CH_2Cl_2 at room temperature, and the reaction progress was followed by GC. Although the reaction was completed with less than 1 eq of IF_5-pyridine-HF to **1a**, a long reaction time was required (Entry 1 in Table 1). When 1.1 eq of IF_5-pyridine-HF was used, the reaction was completed in a shorter time and 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl fluoride **(2a**) was obtained in good yield (Entry 2). The use of 2 eq of IF_5-pyridine-HF resulted in a slight improvement in yield (Entry 3). The ratio of α- and β-isomers in **2a** was found to be in the range of 1.0 : 2.0-2.3, and was independent of the reaction conditions examined (Entries 1-3).

We applied IF_5-pyridine-HF for the synthesis of various glycosyl fluorides as shown in

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Table 2. Various protecting groups of alcohol and diol such as acetate (Entries 1, 2, 7, and 8), benzyl ether (Entry 3), acetonide (Entries 4-6), and benzoate (Entry 5), tolerate the reaction conditions. Silyl ethers, also widely used as the protecting group of alcohols, are sensitivity to fluoride and fluorinating reagents. Therefore, we used IF_5-pyridine-HF to the reaction with a substrate bearing the silyl protecting group. A ribose derivative bearing a *tert*-butyldimethylsilyl group (**1f**) was treated with 1.1 eq of IF_5-pyridine-HF, and the reaction was followed by NMR. After 30 min, **1f** was consumed completely and the desired glycosyl fluoride (**2f**) was formed in 80% yield. However, the desilylated product was also formed in 20% yield. In contrast, when 0.55 eq of IF_5-pyridine-HF was used, the reaction was completed in 30 min and **2f** was formed in 88% yield (Entry 5). Under these conditions, only 7% of the desilylated product was formed. It was also found that IF_5-pyridine-HF could be applied to the synthesis of the 2-amino-2-deoxyglycosyl fluoride derivative (**2g**) (Entry 7) and the disaccharide derivative (**2h**) (Entry 8). In addition to pyranosyl fluorides (**2a**,**b,g,h**), furanosyl fluorides (**2c**-**f**) could be prepared from the corresponding (phenylthio)glycosides by reaction with IF_5-pyridine-HF.

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3. Conclusion

We applied IF_5-pyridine-HF, which is air- and moisture-stable, and easy to use, for the preparation of glycosyl fluorides from corresponding (phenylthio)glycosides. It was found that IF_5-pyridine-HF is suitable for the synthesis of various glycosyl fluorides,

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and common protecting groups of alcohol tolerate the fluorination conditions.

4. Experimental

4.1. General methods

IF_5 in a cyclinder was supplied by Daikin industries, Ltd. Anhydrous HF in a cyclider was purchaed from Stella Chemifa Corporation. IF_5-pyridine-HF was prepared from IF_5 and pyridine-HF by the previously reported method.[17] (Phenylthio)glycosides **1a**,**b**,[19] **1c**,[20] **1d-f,**[21] and **1g,h**[19] were prepared according to the literatures. Glassware can be used for the reaction, but use of Teflon™ or polyethylene ware is recommended.

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4.2. A typical procedure for transformation of (phenylthio)glycoside into glycosyl fluoride using IF_5-pyridine-HF

4.2.1. 2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl fluoride (2a)

To a CH_2Cl_2 solution (2 mL) of IF_5-pyridine-HF (321 mg, 1.0 mmol) was added **1a** (220 mg, 0.5 mmol) at room temperature and the mixture was stirred at room temperature for 18 h. After confirmation of complete consumption of **1a** by GC, the mixture was poured into water (20 mL) and extracted with ether (20 mL X 3). The combined organic layer was washed with aq $NaHCO_3$ and aq $Na_2S_2O_3$, and dried over $MgSO_4$. After concentration, **2a** was isolated by column chromatography (silica

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gel/hexane:Et_2O = 1:1~1:2) in 81% yield as a mixture of α- and β-isomer (1:2.2 determined by ^{19}FNMR).

(α-isomer[22]): White solid. Mp 104-106 °C.

(**β-isomer**[23]): White solid. Mp 79-80 °C.

2,3,4-Tri-*O*-acetyl-D-xylopyranosyl fluoride (2b)

(**α-isomer**[24]): Yellow solid. Mp 84-85 °C.

(**β-isomer**[24]): Yellow solid. Mp 54-55 °C.

2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl fluoride (2c) [25]

Clear liquid.

2,3:5,6-Bis-*O*-(isopropylidene)-α-D-mannofuranosyl fluoride (2d) [11]

Clear liquid.

2,3-Di-*O*-isopropylidene-5-*O*-benzoyl-β-D-ribofuranosyl fluoride (2e) [26]

Clear liquid.

2,3-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl fluoride (2f) [23]

Clear liquid.

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3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucosyl fluoride (2g) [27]

White solid. Mp. 166-167 °C.

2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranosyl fluoride (2h) [28]

White solid. Mp 167-168 °C.

Acknowledgment

We are grateful to Daikin industries, Ltd. for their donation of IF_5.

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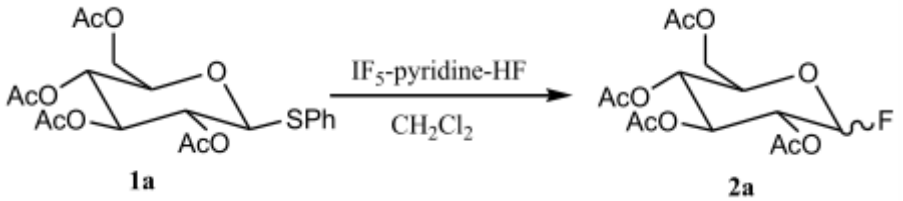
Table 1 Synthesis of glycosyl fluoride **2a** by the reaction of (phenylthio)glycoside **1a** with IF_5-pyridine-HF[a]



1a **2a**

Entry	IF_5-pyridine-HF / **1a**	React time, h	Yield of **2a**, %[b]
1	0.55	33	85 (1:2.0)
2	1.1	20	94 (1:2.2)
3	2.0	18	98 (1:2.2)

[a] The reaction was carried out in CH_2Cl_2 at room temperature.

[b] ^{19}F NMR yield. In prentheses, ratio of α- and ß-isomer.

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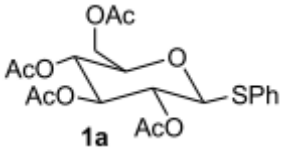
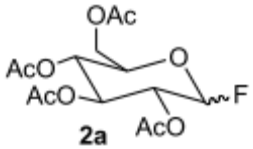
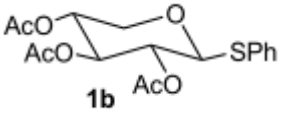
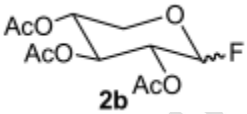
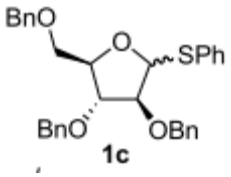
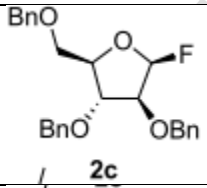
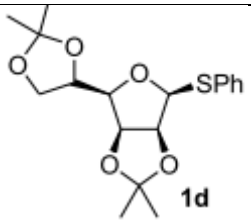
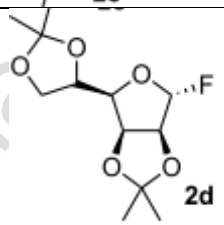
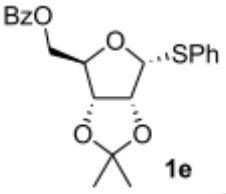
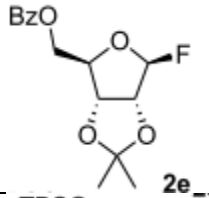
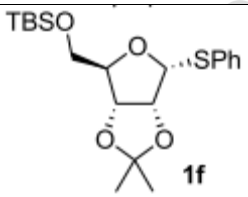
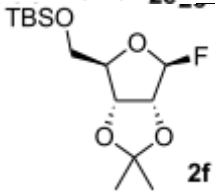
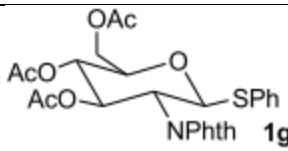
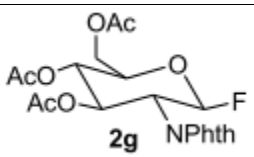
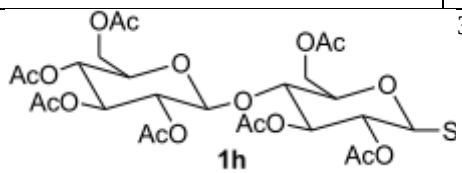
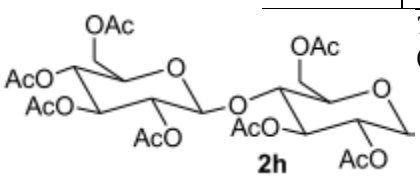
Table 2 Synthesis of glycosyl fluorides from (phenylthio)glycosides by the reaction with IF_5-pyridine-HF[a]

Entry	Substrate **1**	React. Time h	Product **2**	Yield, %[b]
1[c]	 **1a**	18	 **2a**	81(98) (α:β = 1.0:2.2)
2	 **1b**	2	 **2b**	76 (α:β = 1.0:1.5)
3	 **1c**	6.5	 **2c**	77 (β only)
4	 **1d**	2	 **2d**	90 (α only)
5	 **1e**	4	 **2e**	89 (β only)
6[d]	 **1f**	0.5	 **2f**	65 (88[e]) (β only)
7	 **1g**	2	 **2g**	96 (β only)
8	 **1h**	3	 **2h**	73 (β only)

[a] If otherwise not mentioned, the reaction was carried out in CH_2Cl_2 at room temperature using 1.1 eq of IF_5-pyridine-HF.

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[b] Isolated yield. In parentheses, ^{19}F-NMR yield.

[c] 2.0 eq. of IF_5-pyridine-HF was used.

[d] 0.55 eq. of IF_5-pyridine-HF was used.

[e] 7% of desilylated product was also formed.

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