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IPy_2BF_4/HF-Pyridine: A New Combination of Reagents for the Transformation of Partially Unprotected Thioglycosides and *n*-Pentenyl Glycosides to Glycosyl Fluorides

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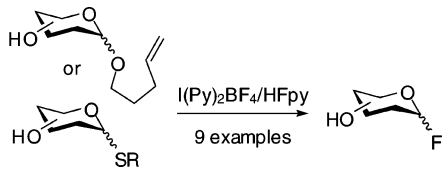

The combination of bis(pyridinium)iodonium (I) tetrafluoroborate (IPy_2BF_4), and hydrogen fluoride pyridine (HF-py) forms an iodine monofluoride (IF) synthetic equivalent that can be used in the preparation of partially unprotected glycosyl fluorides from partially unprotected *n*-pentenyl glycosides and thioglycosides, thus avoiding the need for the protection/deprotection steps normally required in that transformation.

Oligosaccharides are pivotal compounds in many biological recognition processes.[1,2] Consequently considerable research has been directed toward the development of strategies for glycosylation.[3,4] The efficiency of these strategies often relies on the choice of the glycosyl donor[5] and the minimization of protecting-group manipulations.[6] Thioglycosides,[7] *n*-pentenyl glycosides (NPGs),[8] and glycosyl fluorides[9] are reliable glycosyl donors, which can also function as glycosyl acceptors in armed/disarmed,[10] and orthogonal[11] (or semi-orthogonal)[12] glycosylation strategies. 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[13] or by regioselective coupling of polyol glycosyl acceptors.[14] In this context, we believe that the design of methods that allow the direct exchange of anomeric leaving groups between partially unprotected sugar building blocks (glycosyl donors or acceptors) would be useful.[15]

We have been interested in the study of regioselective glycosylation strategies[16] of partially unprotected glycosyl donors with diol acceptors.[17,18] More recently we have described the use of bis(pyridinium)iodonium (I) tetrafluoroborate (IPy_2BF_4)[19] for the transformation of NPGs into glycosyl fluorides (e.g., **1a** → **2**, Scheme 1).[20] A recent report by Huang and Winssinger[21] on the use of IPy_2BF_4 for the transformation **1b** → **2** and for promoting glycosylation of thioglycosides has prompted us to disclose our own results in this area.

On the basis of the similar reactivity displayed by NPGs and thioglycosyl donors toward iodonium-based promoters,[22] and our own experience with these donors,[23] we decided to investigate: (i) the use of IPy_2BF_4 as a promoter for glycosylation of NPGs, (ii) the use of IPy_2BF_4 for the transformation of thioglycosides into glycosyl fluorides (e.g., **1b** → **2**, Scheme 1), and (iii) the transformation of partially unprotected NPGs and thioglycosides to glycosyl fluorides. To the best of our knowledge, no direct method for the transformation of partially

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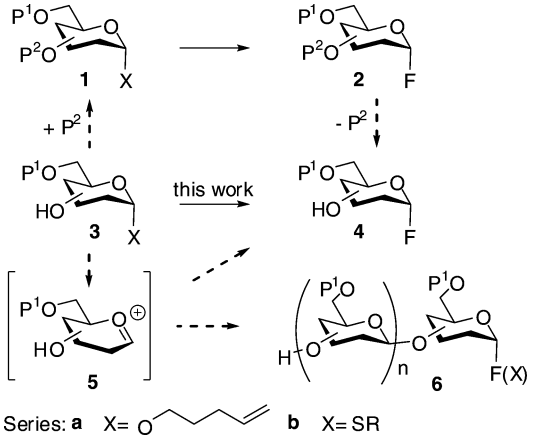
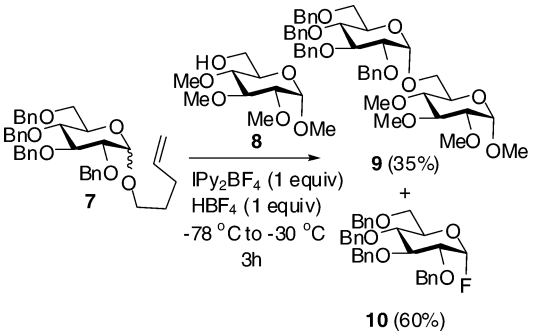
SCHEME 1. Transformation of *n*-Pentenyl Glycosides and Thioglycosides into Glycosyl Fluorides



SCHEME 2. Attempted Glycosylation of 8 with NPG 7 Mediated by IPy_2BF_4

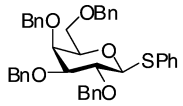
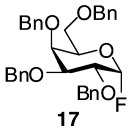
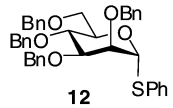
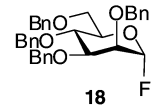
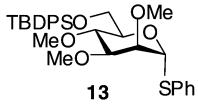
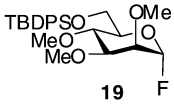
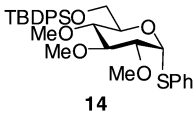
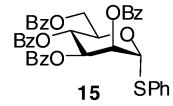
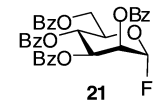
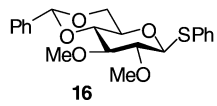
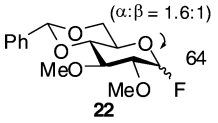


unprotected thioglycosides, or NPGs, into partially unprotected glycosyl fluorides (e.g., **3** → **4**) has been reported. In fact, the standard procedure for such transformation (e.g., **3a**,**b** → **4**, Scheme 1) would require two additional protection-deprotection steps (e.g., **3** → **1** and **2** → **4**, Scheme 1) since the intermediate oxocarbenium ion (**5**) could also experience self-condensation to yield saccharide(s) **6**.

We first studied the reaction of primary acceptor **8** with NPG **7** in the presence of IPy_2BF_4 and HBF_4, in CH_2Cl_2 (Scheme 2). The reaction furnished disaccharide **9** in 35% yield. However, the major reaction product was glycosyl fluoride **10** (60% yield). IPy_2BF_4 is a stable reagent that acts as a mild source of iodonium ions. In the presence of an acid that neutralizes the supply of pyridine molecules[24] IPy_2BF_4 can be contemplated as a synthetic equivalent of iodine monofluoride,[25] and thus, the formation of compound **10** can be explained by the presence of nucleophilic fluoride that competes with the glycosyl acceptor **8** for the oxocarbenium ion.[26]

The formation of compound **10** in Scheme 2, suggested that an exchange of anomeric leaving groups could be performed without tampering with the free OH groups in unprotected NPGs. We then decided to search for reaction conditions that could induce such transformations on NPGs and thioglycosides (e.g., **3a**,**b** → **4**, Scheme 1) without the competing self-

TABLE 1. IPy_2BF_4-Mediated Transformation of Thioglycosides to Glycosyl Fluorides in the Presence of an Acid in CH_2Cl_2 at −40 °C

Entry	Substrate	Acid	Product	Yield (%)
i	 **11**	HBF_4	 **17**	95
ii	**11**	$BF_3{\cdot}Et_2O$	**17**	86
iii	**11**	$Yb(OTf)_3$	**17**	69
iv	 **12**	HBF_4	 **18**	98
v	 **13**	HBF_4	 **19**	85
vi	 **14**	HBF_4	 **20**	94
vii	 **15**	HBF_4	 **21**	99
viii	 **16**	HBF_4	 (α:β = 1.6:1) **22**	64

glycosylation process (e.g., **3** → **6**). The first step was to confirm that thioglycosides could be transformed into glycosyl fluorides under the agency of IPy_2BF_4.[21]

Phenyl 1-thioglycosides **11**−**16** were transformed to glycosyl fluorides by the action of IPy_2BF_4 (see Table 1). HBF_4, $BF_3{\cdot}Et_2O$, and $Yb(OTf)_3$ were evaluated as pyridine scavengers, and better yields of glycosyl fluorides were obtained with the system IPy_2BF_4/HBF_4 (Table 1, compare entries i−iii). These fluorinating conditions were then used with substrates **12**−**16** and proved to be compatible with the presence of benzyl, benzoyl, *tert*-butyldiphenylsilyl, and benzylidene protecting groups (Table 1, entries i−viii).

We next turned our attention to the transformation of partially unprotected NPGs, **23**, **24**, and thioglycosides, **25**, **26**, to glycosyl fluorides (Table 2). When NPGs containing a secondary free OH group were treated with IPy_2BF_4 in the presence of HBF_4 in CH_2Cl_2 at −40 °C, the major reaction products obtained were the expected glycosyl fluorides, although a respectable amount of fluoride disaccharides was also obtained (Table 2, entries i,ii). Phenyl 1-thioglycoside **25**, containing a primary 6-OH free, furnished upon treatment with IPy_2BF_4/HBF_4 fluoride **31** in only 23% yield, the major product of the reaction being anhydro-derivative **32** (Table 2, entry iii). The use of conformationally restricted thioglycoside **26** prevented the formation of the anhydro derivative; however, the sought-for fluoride **33** was still obtained as the minor reaction product (33%

(24) Barluenga, J. *Pure Appl. Chem.* **1999**, *71*, 431−436.
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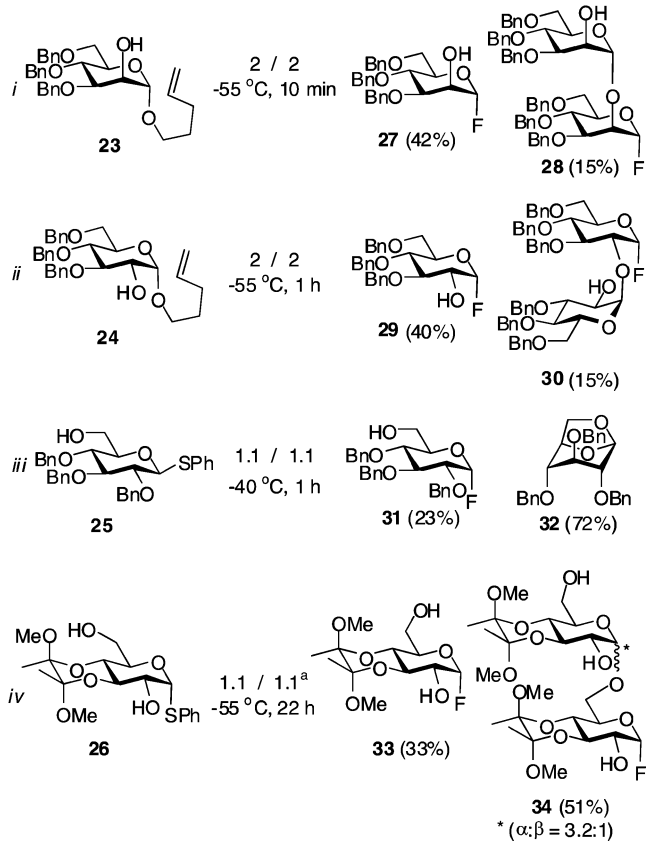
TABLE 2. IPy_2BF_4/HBF_4-Mediated Transformation of Partially Unprotected NPGs and Phenylthioglycosides to Glycosyl Fluorides in CH_2Cl_2



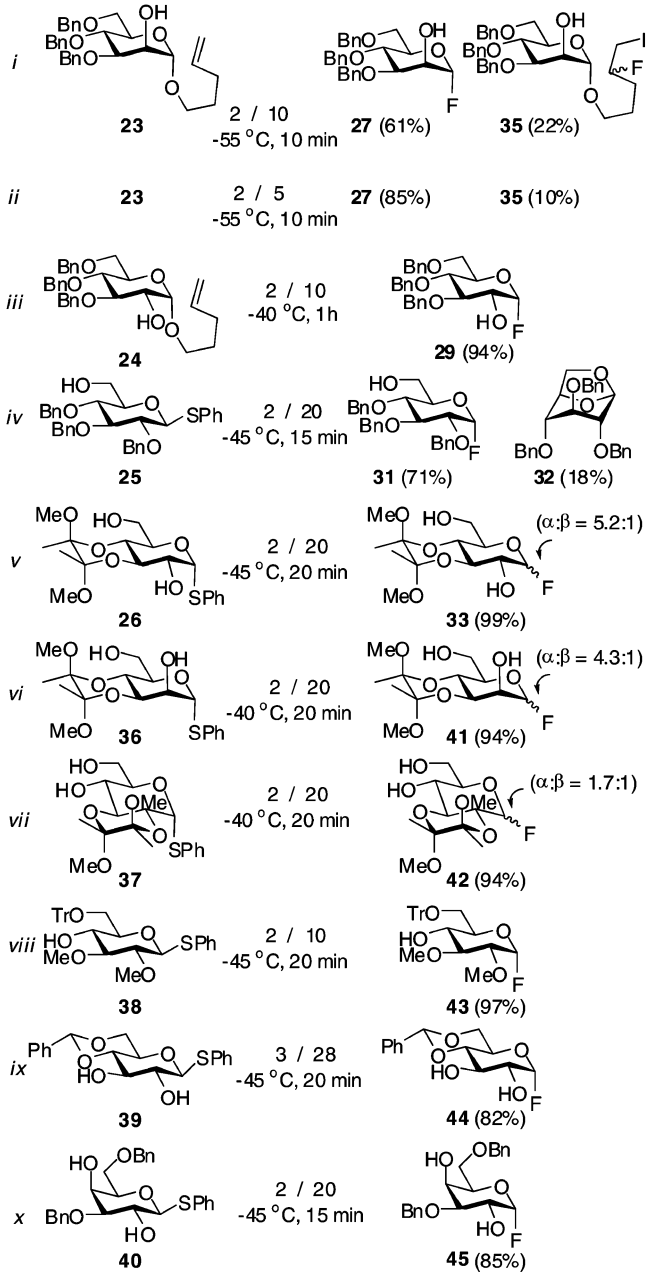
[a] $BF_3.Et_2O$ was used instead of HBF_4

yield) (Table 2, entry iv), and the major observed compound was now disaccharide **34** (51% yield) resulting from self-glycosylation of either **26** or **33** (vide infra).

From the results outlined in Table 2, several conclusions were drawn: (a) the concentration of nucleophilic fluoride in the reaction media is not sufficient to ensure the sole formation of glycosyl fluorides, a tendency even more pronounced when primary OHs were present in the molecule (Table 2, compare entries i, ii with entries iii, iv), (b) HBF_4, that has been reported as a useful promoter for glycosylation of glycosyl fluorides,[27] might not be fully compatible with the final glycosyl fluorides, and thus, the formation of disaccharides could arise either from direct glycosyl coupling of the starting thioglycosides or by acid-catalyzed activation of initially formed glycosyl fluorides.

Along these lines we selected Olah's HF−pyridine complex[28,29] as partner to Barluenga's IPy_2BF_4 in order to accomplish the sought-for transformation. HF−Pyridine complex could play a dual role as the source of additional nucleophilic fluoride and as the acid to neutralize the supply of nucleophilic pyridine. On the other hand, HF−pyridine complex would be harmless to glycosyl fluorides under our reaction conditions.

TABLE 3. IPy_2BF_4/HF−Pyridine-Mediated Transformation of Partially Unprotected NPGs and Phenylthioglycosides to Glycosyl Fluorides, in CH_2Cl_2



Accordingly, we submitted NPGs **23**, **24**, and thioglycosides **25**, **26**, **36**−**40** to the action of IPy_2BF_4 (2 equiv)/HF-pyridine[30] (5−20 equiv) in CH_2Cl_2 at low temperature (−40 to −55 °C). Our results, outlined in Table 3, showed that partially unprotected NPGs and thioglycosides can be successfully transformed

(27) HBF_4, $BF_3{\cdot}Et_2O$, and $Yb(OTf)_3$ have been reported as useful promoters for glycosylation of glycosyl fluorides. See ref 9c.

(28) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872−3881.

(29) HF−pyridine complex has been used as a source of fluoride in the preparation of glycosyl fluorides: (a) Hayashi, M.; Hashimoto, S.; Noyori, R. *Chem. Lett.* **1984**, 1747−1750. (b) Szarek, W. A.; Grynkiewicz, G.; Doboszewski, B.; Hay, G. W. *Chem. Lett.* **1984**, 1751−1754. (c) Bröder, W.; Kunz, H. *Carbohydr. Res.* **1993**, *249*, 221−241. (d) Palme, M.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 959−969. (e) Lee, Y. J.; Lee, B. Y.; Jeon, H. B.; Kim. K. S. *Org. Lett.* **2006**, *8*, 3971−3974.

(30) The reaction of compounds **27**−**32** with the system IPy_2BF_4/HBF_4 normally yielded a mixture of compounds.

to glycosyl fluorides. The reaction of NPGs **23** and **24** furnished glycosyl fluorides **27** and **29**, respectively (Table 3, entries i−iii). The formation of glycosyl fluoride **27**, however, was accompanied by some iodofluorination on the *n*-pentenyl chain to give **35** (Table 3, entry i). Compound **35** was undoubtedly formed by bimolecular fluorination of the cyclopropyliodonium ion intermediate in the cationic cascade arising from NPGs,[8b] (Table 3, entry i). The amount of **35** formed could be reduced by lowering the amount of HF-pyridine employed (Table 3, compare entries i and ii). Reaction of thioglycoside **25** with IPy_2BF_4 (2 equiv)/HF−pyridine (20 equiv), −45 °C, yielded glycosyl fluoride **31** as the major product in 71% yield; however, a minor amount of anhydro sugar derivative **32** (18%), was still present (Table 3, entry iv). The formation of anhydro sugar derivatives could be avoided with the incorporation of Ley's diacetal protecting groups[31,32] (Table 3, entries v−vii). This reaction could be applied to diols (Table 3, entries v−vii, ix,x), and an acid-sensitive trityl protecting group was shown to survive the reaction conditions (Table 3, entry viii).

In summary, we have shown that IPy_2BF_4 can be used in combination with HF−pyridine to successfully convert partially unprotected NPGs and thioglycosides to glycosyl fluorides. This transformation can be useful in block or orthogonal strategies for oligosaccharide synthesis since it reduces the number of protection/deprotection steps in the interconversion of glycosyl acceptors.

Experimental Section

General Procedure for the IPy_2BF_4/HBF_4-Mediated Transformation of Thioglycosides to Glycosyl Fluorides. A solution of bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) (44.6 mg, 0.12 mmol) in dry CH_2Cl_2 (1 mL) under argon and cooled at −40 °C was treated with tetrafluoroboric acid (13 μL, 0.12 mmol). After 5 min, a solution of the thioglycoside (0.10 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added. When all the starting material disappeared, the reaction mixture was diluted with dichloromethane (30 mL) and washed with 10% aqueous sodium thiosulphate containing sodium bicarbonate and water. The organic layer was dried and concentrated, and the residue was purified by flash chromatography using hexane−ethyl acetate mixtures.

General Procedure for the IPy_2BF_4/HF.Py-Mediated Transformation of Partially Protected NPGs and Phenyl 1-Thioglycosides to Glycosyl Fluorides. A solution of bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) (0.2 mmol) in dry CH_2Cl_2 (3 mL) was cooled to the appropriate temperature (See Table 3). HF−pyridine complex (5, 10, or 20 equiv) was then added, and the resulting solution was stirred for 5 min. A solution of NPG or phenylthioglycoside (0.1 mmol) in dry CH_2Cl_2 (2 mL) was then added dropwise. The resulting solution was then stirred at low temperature (as indicated in Table 3). The reaction was then diluted with methylene chloride (20 mL), and the resulting solution was carefully added to an aqueous solution containing $NaHCO_3$ and $Na_2S_2O_3$. The resulting layers were separated, and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with saturated aqueous NaCl. The resultant organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane−ethyl acetate) afforded the corresponding glycosyl fluorides.

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Supporting Information Available: Preparation and physical data for compounds **17**−**22**, **27**−**34**, and **41**−**45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897−3899.