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PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination Reagent

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Supporting Information

ABSTRACT: We report an inexpensive, thermally stable deoxyfluorination reagent that fluorinates a broad range of alcohols without substantial formation of elimination side products. This combination of selectivity, safety, and economic viability enables deoxyfluorination on preparatory scale. We employ the [^{18}F]-labeled reagent in the first example of a no-carrier-added deoxy-radiofluorination.

Organofluorine compounds are featured prominently throughout industry owing to the unique properties that fluorine substitution confers on organic molecules.[1,2] Notably, in the context of drug design, the introduction of carbon−fluorine bonds can dramatically improve the metabolic stability, solubility, and activity of pharmaceutical candidates.[3] Deoxyfluorination of alcohols is one of the most attractive methods for installing aliphatic C−F bonds due to the abundance and accessibility of alcohol-containing precursors.[4−7] In this technique, a deoxyfluorination reagent generates both an activated leaving group and a nucleophilic fluoride source that react *in situ* to afford product (Figure 1). Although this transformation may also be achieved through multistep sequences,[8] a one-pot deoxyfluorination often proceeds under milder conditions with broader functional group tolerance.

Introduced in the 1970s, diethylaminosulfur trifluoride (DAST) remains the most popular deoxyfluorination reagent due to its availability and general scope. DAST readily fluorinates alcohols and will also convert ketones and aldehydes to geminal difluorides.[5b,c] However, the reagent's cost and propensity for violent decomposition render it unsuitable for process chemistry.[9] Furthermore, DAST reactions feature limited functional group tolerance and afford elimination side products that complicate purification (Figure 1A). Much effort has been dedicated toward developing thermally stable variants such as Deoxo-Fluor, XtalFluor, and Fluolead,[5d−f] but these options are more expensive and offer only marginal improvements in chemoselectivity. The recently disclosed PhenoFluor exhibits remarkable versatility in the late-stage fluorination of complex natural products, but its high cost and poor shelf stability hinder widespread adoption.[6b] In addition, the inaccessibility of no-carrier-added ^{18}F variants of all of these reagents has precluded adaptation of this powerful transformation to radiolabeling procedures.

Our goal was to identify an inexpensive, operationally convenient, stable, and chemoselective deoxyfluorination reagent that would also be amenable to deoxy-radiofluorination.

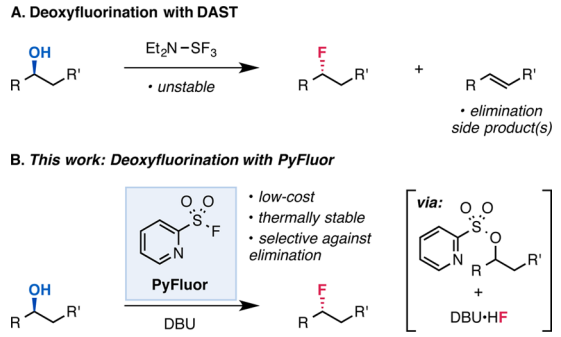

Figure 1. (a) The popular deoxyfluorination reagent DAST frequently affords elimination side products and displays poor thermal stability. (b) PyFluor is a stable and affordable alternative that demonstrates high selectivity against elimination, thus enabling rapid and facile purification.

In this paper, we report a new reagent, 2-pyridinesulfonyl fluoride (PyFluor), which satisfies these criteria (Figure 1B). Previously, our laboratory developed catalytic hydrofluorinations wherein nucleophilic fluoride was generated via esterification of benzoyl fluoride with a sacrificial alcohol.[10] We speculated that increasing the electron-withdrawing nature of the acyl fluoride might instead lead to substitution of the newly formed ester, resulting in a formal deoxyfluorination. The utility of preformed sulfonate esters in multistep fluorination and radiofluorination reactions led us to the investigation of sulfonyl fluorides. Although Vorbrüggen has reported the use of perfluorobutanesulfonyl fluoride (PBSF),[7b] this reagent has failed to gain traction because it produces copious quantities of elimination side products that can render recrystallization or chromatographic separation impossible.[11] Furthermore, in the presence of amines and heterocycles, PBSF liberates gaseous perfluorobutane that can lead to dangerous pressure spikes, making this reagent no more attractive than DAST from a safety perspective.[12] Notwithstanding, we hypothesized that a stable, general, and selective deoxyfluorination using an arylsulfonyl fluoride could be identified based on early literature highlighting their stability toward reduction, hydrolysis, and thermolysis.[13]

We evaluated a broad range of sulfonyl fluorides in the fluorination of alcohol **1** (Table 1; see Supporting Information (SI)). In combination with the amidine base 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), PBSF furnished product **2** in 57% yield with 10% elimination side product, a selectivity of 6:1 that is

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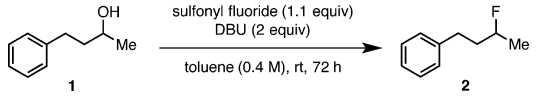
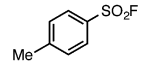
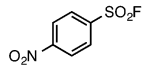
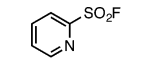
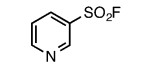
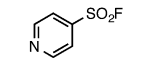
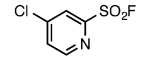
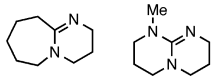
Table 1. Sulfonyl Fluorides as Deoxyfluorination Reagents



1 2

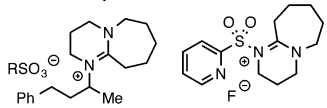
entry	reagent	yield (%)[a]	selectivity[b] (*fluorination : elimination*)
1	DAST	71[c]	4:1
2	Deoxo-Fluor	72[d]	5:1
3		57	6:1
4		21	17:1
5		72	12:1
6		78	20:1
7		**79**	**>20:1**
8		74	13:1
9		70	12:1
10		80	>20:1

Optimal bases



DBU MTBD

Reaction side products



3 4

[a]Yield of **2** determined by GC using 1-fluoro-naphthalene as an internal standard; average of two runs. [b]Ratio of **2** to combined elimination side products as determined by GC. [c]1.8 equiv in CH_2Cl_2, 0 °C; ref 15. [d]1.2 equiv in CH_2Cl_2, −78 °C; ref 14.

consistent with previous reports (entry 3).[14] We were pleased to find that most electron-deficient aryl- and heteroaryl-sulfonyl fluorides outperformed PBSF in terms of both yield and selectivity. Notably, 2-pyridinesulfonyl fluoride afforded **2** in 79% yield with greater than 20:1 selectivity (entry 7). By comparison, commercially available DAST and Deoxo-Fluor are markedly less selective, providing 13−19% elimination (entries 1, 2).[14,15] Previous reports have suggested that 2-pyridinesulfonate esters can act as nucleophile-assisted leaving groups in substitution reactions; however the success of both 3- and 4-pyridine-sulfonyl fluorides indicates that pyridine serves primarily as an inductive electron-withdrawing group (entries 8, 9).[16] Consistent with this proposal, incorporation of electron-withdrawing substituents on the pyridine does not attenuate reactivity and may lead to modest improvements in yield (entry 10); however, we chose to pursue our studies with 2-pyridinesulfonyl fluoride (hereafter referred to as PyFluor), as we felt it represented the best combination of cost (*vide infra*) and efficiency.

In our investigation of reaction conditions, we found that strong amidine and guanidine bases such as DBU and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) are uniquely effective. Optimal conditions employ just 1.1 equiv of PyFluor with 2 equiv of base. Interestingly, the reaction is not highly solvent dependent; toluene and cyclic ethers perform best, but reasonable yields are obtained in DMSO and acetonitrile. It is also noteworthy that this method does not require exclusion of air or moisture. Over the course of a typical reaction, the sulfonate ester forms quantitatively in minutes and is then gradually converted to product within 48 h (see SI for optimization and reaction profile). The only side product detected by LC-MS is cation **3**, which arises from nucleophilic attack by DBU on the sulfonate ester intermediate and accounts for the mass balance.

DBU and MTBD are known to behave as both Brønsted bases or nucleophilic acyl transfer catalysts.[17] When PyFluor is mixed with DBU, complex **4** is observed by LC-MS, but it forms several orders of magnitude slower than the sulfonate ester under standard reaction conditions. Moreover, **4** is incompetent for deoxyfluorination of alcohol **1**. Taken together, these data suggest that DBU and MTBD function principally as Brønsted bases. We propose that deoxyfluorination proceeds by base-assisted addition of the substrate alcohol to the sulfonyl fluoride. The protonated base then stabilizes the developing fluoride ion leaving group. This proposal is in line with observations by Sharpless that the S−F bond in sulfonyl fluorides must be activated by a protic species in order to be labile.[18] Sulfonyl transfer produces the reactive amidine hydrogen fluoride, which mediates fluorination of the sulfonate ester intermediate.

With optimal conditions in hand, we proceeded to delineate the reagent's substrate scope (Table 2). PyFluor serves as a general deoxyfluorination reagent for both primary (**5**) and secondary alcohols (**2**). Complex biomolecules including carbohydrates (**6**, **7**), steroids (**8**), and amino acids (**9**) can be fluorinated in high yield. PyFluor also tolerates a broad range of basic functionality including phthalimides (**10**), heterocycles (**11**, **21**), and protected and even unprotected amines and anilines (**9**, **12**−**15**). Furthermore, difluorination can be achieved in good yield (**16**). Most reactions proceed at room temperature, although cyclic or sterically encumbered substrates may require moderate heating. Additionally, the diastereoselectivity observed with **8**, **9**, and **14** indicates that fluorination occurs with inversion and without epimerization.[19] These results compare favorably to those obtained using commercially available reagents and highlight the potential of the method for late-stage diversification of natural products and drug-like molecules.[20]

A number of examples of PyFluor's chemoselectivity are also of note: Primary and secondary alcohols can be fluorinated in the presence of tertiary alcohols (**17**). Substrates possessing carbonyls do not undergo competing *gem*-difluorination or form acyl fluorides as with DAST and its derivatives.[5] Homobenzylic alcohols (**20**, **21**), which are highly susceptible to elimination with DAST, perform well under the standard conditions, although some elimination is observed (8−10%). Unhindered benzylic alcohols (**22**, **23**) also deliver fluorinated product, albeit in only moderate yield due to competitive nucleophilic attack by the base on the sulfonate intermediate. In contrast, β-hydroxy carbonyl compounds bearing acidic α protons (**24**) afford exclusively elimination, exposing a limit of the reagent's chemoselectivity. Aside from these exceptions, most substrates do not generate elimination side products. This results in trivial purifications; the crude reaction mixture can simply be flushed through a short silica column to remove the ionic side products. As a demonstration of scalability, alcohol **1** can be fluorinated on 5 g scale with no diminution in yield (79%).

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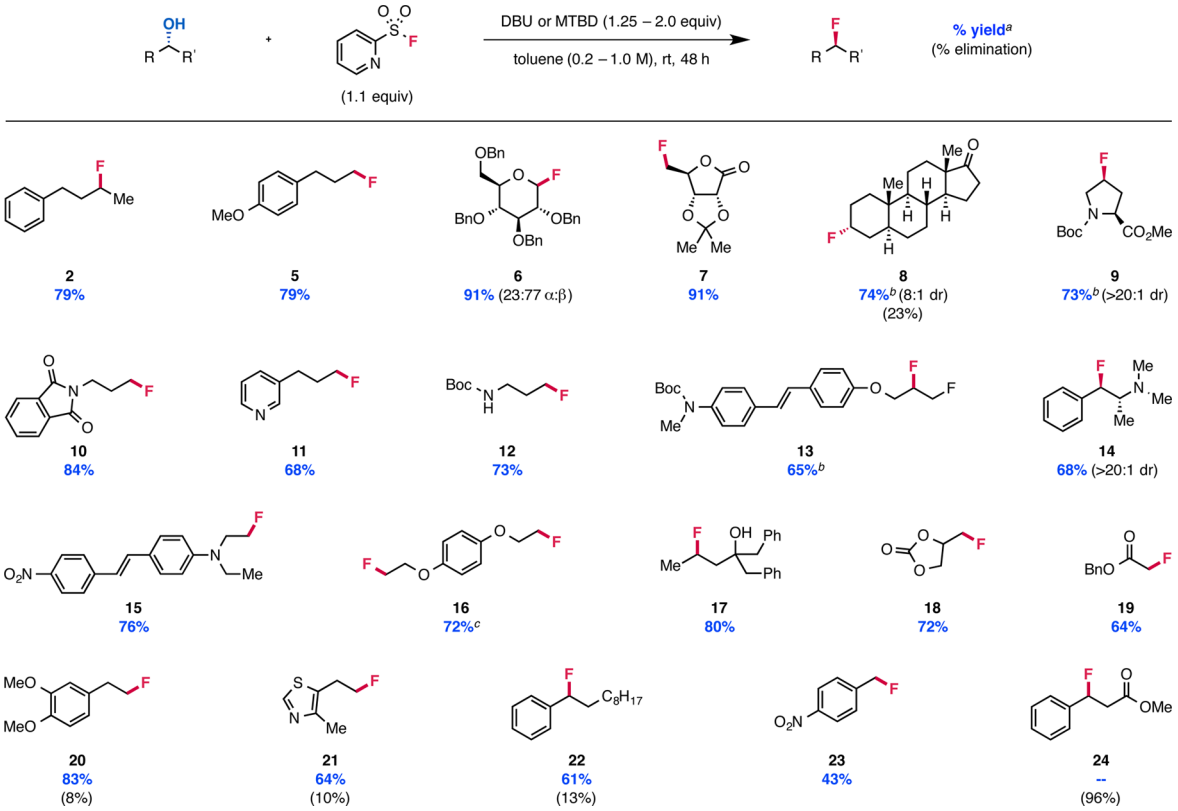
Table 2. Scope of the Deoxyfluorination with PyFluor



[a]Isolated yield of fluorinated product; average of two runs. Experiments conducted on 0.1–1 mmol scale. [b]Heated at 50 °C. [c]2.1 equiv of PyFluor, 3.5 equiv of base.

The positive attributes of PyFluor extend beyond its reactivity and selectivity profile. PyFluor can be synthesized on multigram scale via the oxidation of 2-mercaptopyridine and halide exchange with potassium bifluoride (Figure 2). This unoptimized procedure consumes only $180 of materials per mol of reagent produced, which suggests that PyFluor could be manufactured at a price competitive to that of DAST ($443 per mol, Oakwood).[21] Yet unlike DAST, PyFluor is remarkably stable. The reagent is a low-melting solid (mp 23–26 °C) that can be handled and stored on the benchtop for over 30 days with no detectable decomposition. Furthermore, the sulfonyl fluoride does not hydrolyze in aqueous emulsion and is even stable on silica gel. DAST, however, must be refrigerated and will react violently with trace moisture. Almost all reported deoxyfluorination reagents exhibit exothermic thermal decomposition; for example, differential scanning calorimetry (DSC) indicates that DAST decomposes explosively at 155 °C with an exotherm of 63 kcal/mol.[9b] In contrast, PyFluor does not undergo exothermic decomposition in the range 0–350 °C (see SI for DSC data). Taken as a whole, PyFluor demonstrates a substantially better safety profile than other low-cost deoxyfluorination reagents.

Deoxyfluorination with PyFluor is also translatable to ^{18}F radiolabeling (Figure 3). Substitution of alkyl sulfonates with [^{18}F]KF/K_{222} forms the basis for the majority of radiotracer syntheses in PET imaging applications.[22] Nevertheless, this methodology fails in the presence of numerous biologically relevant functional groups, requires high temperatures to induce reasonable rates (>100 °C), and often leads to elimination products that are challenging to separate from the radiolabeled target. A ^{18}F-variant of a deoxyfluorination remains an attractive but elusive alternative approach to aliphatic C–^{18}F bond formation. Thus far, all reported deoxy-radiofluorinations require a ^{19}F carrier in the form of an unlabeled reagent in order to generate enough activated electrophile to react with the nanomolar quantities of ^{18}F available under labeling conditions.[23] Furthermore, deoxyfluorination reagents featuring multiple reactive fluorine equivalents (such as DAST) cannot be made isotopically pure, again due to low ^{18}F concentration. Overall, these methods produce radiolabeled products with low specific activity (i.e., a high concentration of stable isotope). In preliminary studies, we found that reaction of 2-pyridinesulfonyl chloride with [^{18}F]KF/K_{222} at 80 °C for 5 minutes afforded [^{18}F]PyFluor in 88% radiochemical conversion (RCC).[24] Using

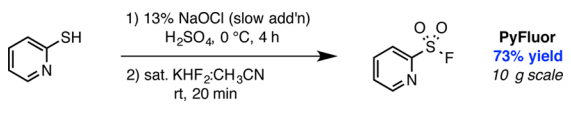


Figure 2. Multigram synthesis of PyFluor.

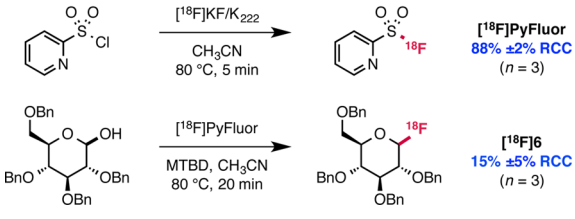


Figure 3. Radiosynthesis of [^{18}F]PyFluor and its application to deoxyradiofluorination.

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this reagent, we were able to achieve deoxy-radiofluorination under comparatively mild conditions, delivering [^{18}F]**6** in 15% RCC after 20 min at 80 °C. This exciting proof of concept represents the first example of a no-carrier-added deoxy-radiofluorination. By performing both the reagent synthesis and deoxy-radiofluorination in a single pot, the unreacted 2-pyridinesulfonyl chloride enables stoichiometric formation of the sulfonate intermediate, thus obviating the need for carrier addition. Moreover, [^{18}F]**6** is inaccessible via conventional radiofluorination methods owing to the instability of the tosylate precursor.[25] This labeling protocol could be particularly useful with substrates for which the sulfonate ester cannot be isolated.

In conclusion, we have developed a low-cost deoxyfluorination reagent that exhibits high chemical and thermal stability. In addition to tolerating a wide range of functionality, PyFluor is highly selective against elimination, allowing for straightforward purifications. Although this method requires longer reaction times and basic conditions, we expect that it will complement existing methods in laboratory screening. Furthermore, we envision that PyFluor will enable preparatory fluorination of alcohols on previously unattainable scale. Finally, we have demonstrated the first example of a no-carrier-added deoxy-radiofluorination with [^{18}F]PyFluor. Our efforts are ongoing to optimize this procedure and interrogate its scope for PET imaging applications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, additional reaction optimization, and spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06307.

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Notes

The authors declare no competing financial interest.

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(19) Deoxyfluorination of enantioenriched alcohol **1** afforded inverted product **2** with 94% enantiospecificity; see SI for details.

(20) As another comparison of PyFluor to commercially available deoxyfluorination reagents, DAST affords product **8** in 47% yield with 44% elimination side product whereas PhenoFluor generates **8** in 84% yield with 11% elimination (ref 6b). Bird, T. G. C.; Fredericks, P. M.; Jones, E. R. H.; Meakins, G. D. *J. Chem. Soc., Chem. Commun.* **1979**, 65.

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