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AlkylFluor: Deoxyfluorination of Alcohols

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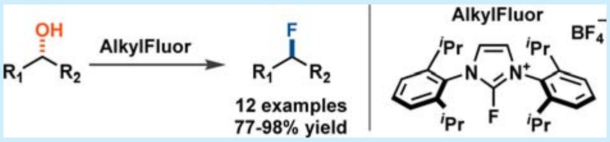
Supporting Information

ABSTRACT: A practical, high-yielding method for the deoxyfluorination of alcohols is presented using AlkylFluor, a novel salt analogue of PhenoFluor. AlkylFluor is readily prepared on multigram scale and is stable to long-term storage in air and exposure to water. The practicality and applicability of this method is demonstrated with a variety of primary and secondary alcohol substrates.



PhenoFluor is a versatile and capable deoxyfluorination reagent, able to transform both phenols and alcohols to the corresponding aryl and alkyl fluorides, respectively, with a broad substrate scope and high functional group tolerance.[1,2] However, PhenoFluor is readily hydrolyzed by ambient moisture and requires special care in storage. Recently, PhenoFluorMix, which does not hydrolyze in air, has been developed. PhenoFluorMix is commercially available and enables operationally practical arene deoxyfluorination (Figure 1).[3] The presence of two chloride equivalents, however, renders it unsuitable for deoxyfluorination of aliphatic alcohols, due to competitive deoxychlorination. Here, we present a new bench-stable reagent, AlkylFluor, capable of efficient, practical deoxyfluorination of alcohols. Deoxyfluorination with AlkylFluor offers higher yields and a broader substrate scope than conventional deoxyfluorination reagents.

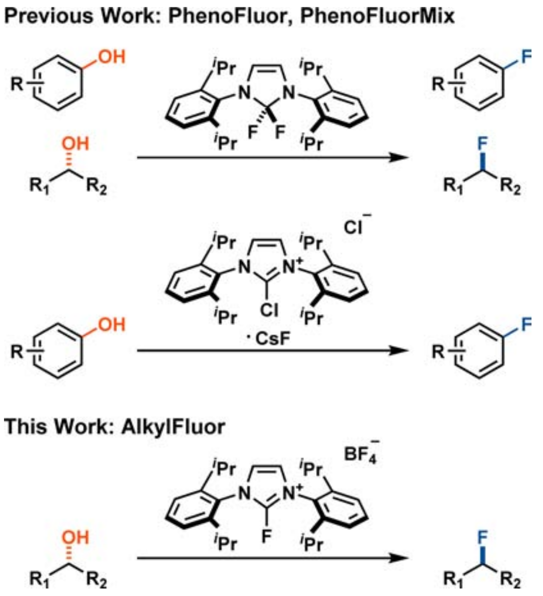
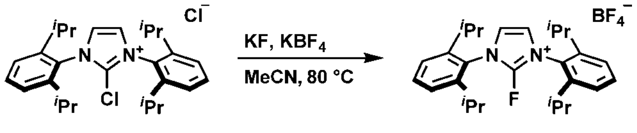


Figure 1. Comparison of AlkylFluor with PhenoFluor and PhenoFluorMix.

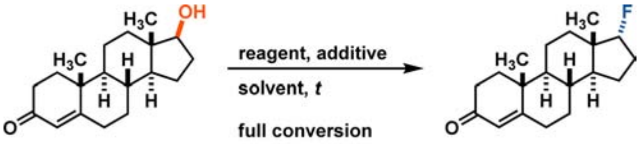


1

AlkylFluor
83%, 18.8 g

Figure 2. Preparation of AlkylFluor.

Table 1. Comparison with Other Commercial Reagents



3

4

reagent	additive	solvent	t(°C)	yield (%)[a]
DAST		DCM	0 → 23	17
XtalFluor-M	DBU	DCM	0 → 23	7
XtalFluor-M	NEt_3-3HF	DCM	0 → 23	10
PyFluor	DBU	toluene	80	7
PhenoFluorMix		toluene	80	4[c]
AlkylFluor	**KF**	**dioxane**	**80**	**50**
AlkylFluor	**CsF**	**toluene**	**80**	**79**[b,c]

[a]Yields were determined by ^{19}F NMR with benzotrifluoride as an internal standard. [b]CsF and AlkylFluor preheated at 100 °C. [c]Isolated yield.

The first generation of practical deoxyfluorination reagents is the "S–F" reagents, comprising DAST and later derivatives such as Deoxo-Fluor, XtalFluor, and Fluolead.[4,5] While these reagents allow access to simple alkyl fluorides, they often

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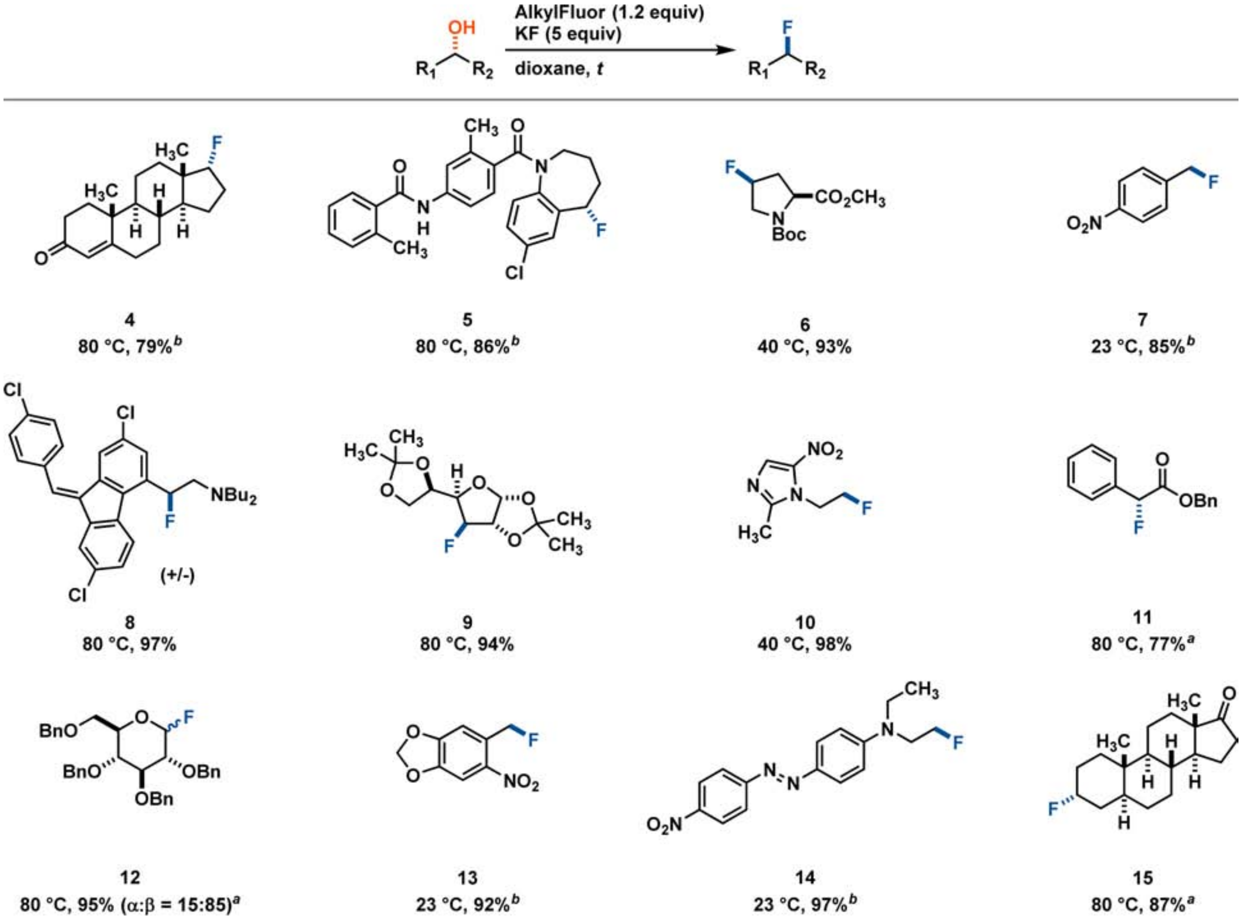
Scheme 1. Deoxyfluorination of Alcohols with AlkylFluor



[a] Ten equivalents of KF used. [b] CsF used instead of KF, preheated with AlkylFluor at 100 °C in toluene.

exhibit insufficient functional group tolerance and chemoselectivity for selective deoxyfluorination of small molecules with multiple functional groups.[1b] Additionally, their thermal instability and risk of explosion presents a significant safety hazard.[6] PyFluor, recently reported by Doyle and co-workers, is in our opinion a promising alternative for practical deoxyfluorination.[7] With high chemoselectivity and shelf stability, it overcomes many of the limitations of earlier reagents and is inexpensive. Nevertheless, reaction with PyFluor requires Brønsted bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene (MTBD) to proceed. These bases can act as nucleophiles, competing with fluoride and diminishing yield, especially for sterically challenging or functionally complex substrates.[7] By contrast, reaction with AlkylFluor requires only fluoride as a base and can access alkyl fluorides that cannot be easily accessed with other reagents. Although this advance in reactivity is offset by the cost of manufacturing AlkylFluor, we believe that AlkylFluor will find its place as a useful reagent for those aliphatic deoxyfluorination reactions that cannot be addressed with other commercially available reagents.

Inspired by the stability of the chloroimidazolium salt **1** and its successful application to deoxyfluorination of phenols with PhenoFluorMix, we hypothesized that a monofluoroimidazolium salt analogue of PhenoFluor might allow access to a more practical reaction for the deoxyfluorination of aliphatic alcohols. AlkylFluor is readily prepared on decagram scale in a single step from commercially available chloroimidazolium chloride **1** (Figure 2). We hypothesize that this reaction favors formation of the monofluoroimidazolium AlkylFluor over PhenoFluor due to the retention of aromaticity, as well as the presence of a large excess of potassium tetrafluoroborate. AlkylFluor is stable at room temperature under ambient atmosphere for several months with no detectable decomposition. It is not hydrolyzed in aqueous suspension and as such is much more easily handled than PhenoFluor itself.

We evaluated the reactivity of several commercial deoxyfluorination reagents with testosterone (**3**) as substrate and compared the reactivity to that of AlkylFluor (Table 1). Testosterone is a challenging substrate for deoxyfluorination primarily due to the steric congestion at the neopentyl-like secondary alcohol. In addition, testosterone contains an enone functional group, which can lead to undesired side reactivity with reagents that display low chemoselectivity. The highest yield of fluorodeoxytestosterone (**4**) obtained with a conventional commercial reagent was 17% with DAST, along with several other unidentified side products. All other commercial reagents gave less than 10% fluorination under reported standard conditions, despite full substrate conversion. PyFluor shows no detectable product under the reported conditions (50 °C, 48 h), and only 7% when the reaction temperature was increased to 80 °C. PhenoFluorMix affords primarily chlorodeoxytestosterone (81% yield), with only 4% yield of **4** (see Supporting Information for details). AlkylFluor, by

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contrast, affords **4** in up to 79% yield and, generally, can enable deoxyfluorination of challenging substrates that cannot be deoxyfluorinated by other reagents, such as PyFluor.

In optimizing the deoxyfluorination reaction with AlkylFluor, we found two complementary reaction protocols. Most alcohols react directly with AlkylFluor in satisfactory yield, in the presence of excess fluoride with mild heating. Potassium fluoride was found to be generally the best fluoride source, and 1,4-dioxane the best solvent. Certain challenging substrates give low yields under these conditions, however. For these cases, we found that AlkylFluor can be converted to PhenoFluor *in situ* by preheating with cesium fluoride in toluene before the addition of the alcohol substrate (see Supporting Information for details). This reaction modification can increase yield, often dramatically, for otherwise low-yielding substrates. While it adds an additional manipulation, it allows access to the full scope of fluorination with PhenoFluor without the associated difficulties of storage and handling. Testosterone, for example, is fluorinated in 50% yield by direct reaction with AlkylFluor, but in 79% yield by preformed PhenoFluor (Table 1). Deoxyfluorination with AlkylFluor generally proceeds cleanly, with only elimination as a minor side reaction for certain alcohols. For optimal results, all reactions should be performed under anhydrous conditions with dried solvents. Alkali metal fluoride salts absorb moisture from air but can be sufficiently dried immediately prior to use by heating under vacuum (100−120 °C, 1 h).

Fluorination with AlkylFluor is applicable to a variety of small molecule classes (Scheme 1), including carbohydrates (**9**, **12**), amino acids (**6**), steroids (**4**, **15**), and pharmaceutical compounds (**5**, **8**, **10**). Carbonyl functionality is well tolerated, including ketones, esters, amides, and carbamates, as well as protected and unprotected amines, acetals, heterocycles, and azo groups.

In conclusion, we have developed a new, bench-stable reagent that allows access to convenient and practical deoxyfluorination of alcohols. AlkylFluor is insensitive to moisture and air. Deoxyfluorination with AlkylFluor demonstrates a broad substrate scope and high functional group tolerance, larger than with any other commercially available reagent, and can be performed on the bench. We expect that this method will provide easy and rapid access to a broad range of late-stage fluorinated molecules once AlkylFluor is commercially available.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03086.

> Detailed experimental procedures and spectroscopic characterization for all new compounds (PDF)

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Notes

The authors declare the following competing financial interest(s): T.R. may financially benefit from sales of AlkylFluor.

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