OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Room Temperature Deoxyfluorination of Benzaldehydes and α-Ketoesters with Sulfuryl Fluoride and Tetramethylammonium Fluoride

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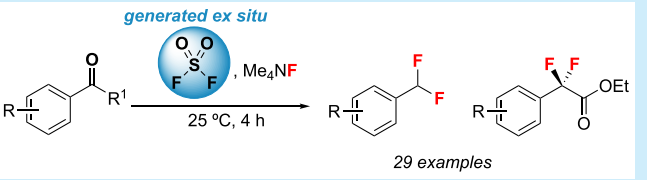
Supporting Information

ABSTRACT: A method for the room temperature deoxyfluorination of benzaldehydes and α-ketoesters using sulfuryl fluoride and Me_4NF is described. A large scope of aryl and heteroaryl substrates is demonstrated, and this method compares favorably to other common deoxyfluorination methods for many substrates.



Deoxyfluorination reactions are powerful methods for the installation of fluorine atoms into organic molecules.[1] The most widely used deoxyfluorination reagent is DAST (diethylamino sulfur trifluoride), which was originally reported in 1973.[2] Over the past four decades, a variety of next-generation alternatives have been developed, including Deoxofluor,[3] Fluolead,[4] Xtalfluor,[5] PBSF[6] (perfluorobutane sulfonyl fluoride), PhenoFluor,[7] DFMBA[8] (*N*,*N*-diethyl-α,α-difluoro-(*m*-methylbenzyl)amine), DFI[9] (2,2-difluoro-1,3-dimethylimidazolidine), and PyFluor[10] (see Figure 1 for representative examples). All of these are highly effective for the conversion of primary and secondary alcohols to alkyl fluorides. Many have also been applied to the deoxyfluorination of aldehydes, ketones, and/or phenols.[2b,3] However, despite their utility, these existing deoxyfluorinating reagents remain limited by some combination of thermal instability, high cost, and limited substrate scope. For these reasons, they are commonly used on a laboratory scale, but are limited in the context of process-scale deoxyfluorination reactions.

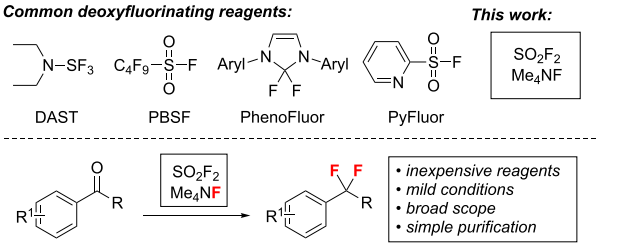


Figure 1. (a) Common, commercially available deoxyfluorination reagents. (b) Deoxyfluorination of benzaldehydes using SO_2F_2 and Me_4NF (*this work*).

We recently demonstrated that the inexpensive commodity chemical sulfuryl fluoride (SO_2F_2) can be utilized for the deoxyfluorination of phenol substrates. In combination with tetramethylammonium fluoride (Me_4NF), SO_2F_2 effectively converts electronically diverse phenols to the corresponding aryl fluorides under mild conditions.[11] We hypothesized that the inexpensive and thermally stable combination of SO_2F_2/Me_4NF[12] should also enable other deoxyfluorination reactions, and we initially targeted the deoxyfluorination of (hetero)-aromatic aldehydes. This transformation is known with other deoxyfluorinating reagents,[2b,3] but it has been less extensively studied than analogous alcohol deoxyfluorination reactions. Indeed, many published examples are limited to simple substrates (e.g., benzaldehyde).[13] Notably, the difluoromethyl-substituted (hetero)arene products are of high interest in medicinal and agricultural chemistry.[14,15] Herein, we demonstrate that the combination of SO_2F_2 and Me_4NF is effective for the room temperature deoxyfluorination of a wide scope of aryl and heteroaryl aldehydes as well as α-ketoesters. Furthermore, direct comparison to DAST reveals that SO_2F_2/Me_4NF affords comparable or significantly enhanced yields for most aldehyde and α-ketoester substrates.

Our initial studies focused on the conversion of 4-bromobenzaldehyde (**1a-Ald**) to 1-bromo-4-(difluoromethyl)-benzene (**1a**) under conditions similar to those for the deoxyfluorination of phenols [1.5 equiv of SO_2F_2 (stock solution in DMF), 3 equiv of Me_4NF in DMF at 25 °C for 24 h].[11b] As shown in Table 1, entry 1, this reaction afforded **1a** in 56% yield. While SO_2F_2 is an inexpensive commodity chemical, it is also a toxic gas that can be challenging to handle on a laboratory scale. As such, we also explored a recently reported

Received: January 5, 2019

DOI: 10.1021/acs.orglett.9b00054
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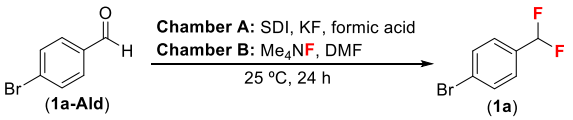
Table 1. Optimization of the Deoxyfluorination of 1a-Ald with SO_2F_2 and Me_4NF



entry[a]	equiv of Me_4NF	equiv of SO_2F_2	yield (%)
1[b]	3	1.5	56
2	3	1.5	68
3	4	2	91
4[c]	4	2	90
5[d]	4	2	85
6[e]	4	2	42

[a]General conditions: (Chamber A) SDI (0.2 mmol, 2 equiv), KF (0.4 mmol, 4 equiv) in formic acid (0.2 mL); (Chamber B) **1a-Ald** (0.1 mmol, 1 equiv), Me_4NF (0.2 mmol, 2 equiv), DMF (0.5 mL) at 25 °C for 24 h. All reactions were set up under anhydrous conditions. Yields were determined via ^{19}F NMR spectroscopy using 4-fluoroanisole as the internal standard. [b]Using a stock solution of SO_2F_2 (0.14 M) in DMF. [c]Reaction time: 4 h. [d]Isolated yield. [e]Reagents weighed on benchtop.

procedure for the *ex situ* generation of SO_2F_2 in a two-chamber system using commercially available 1,1′-sulfonyldiimidazole (SDI), KF, and acid.[16] As shown in Table 1, entry 2, using *ex situ* SO_2F_2 generation under otherwise identical conditions afforded **1a** in 68% yield. DMF proved to be the optimal solvent (see Table S1 for a solvent screen). Increasing the equivalents of Me_4NF and SO_2F_2 to 4 and 2, respectively, resulted in a 91% yield of **1a** (entry 3). Finally, the reaction time could be reduced to just 4 h with minimal impact on the yield (entry 4, 90%). Notably, it is important that this transformation be conducted under anhydrous conditions, due to the water sensitivity of Me_4NF. For example, when the reagents were weighed on the benchtop, rather than in an inert-atmosphere glovebox, the yield dropped to 42% under otherwise analogous conditions (entry 6).

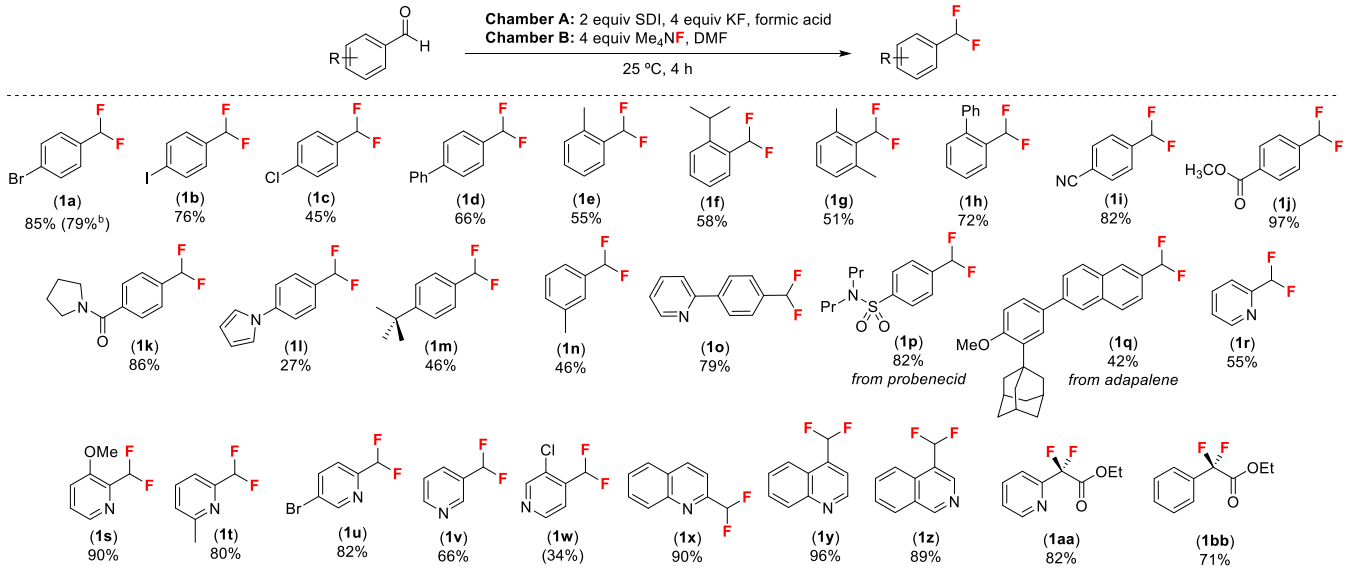
Product **1a** was isolated in high yield from the two-chamber reaction following chromatographic purification on silica gel (85% yield on 0.2 mmol scale and 80% yield on 1 mmol scale). Furthermore, this transformation proceeds in comparable yield using a stock solution of SO_2F_2 in DMF, conditions that better reflect how these reagents would be used on process scale.[17] This latter procedure afforded a 79% isolated yield of **1a** on 5 mmol scale.

We next explored the substrate scope of this deoxyfluorination reaction (Scheme 1). Substitution at the *ortho* (products **1e−h**) position as well as aryl chloride, bromide, and iodide substituents (products **1a−c**) were well-tolerated. These features render this method complementary to many transition metal-catalyzed cross-couplings that form such difluoromethyl arene products.[18] In addition, the simple purification procedure offers a major advantage over cross-coupling approaches to analogous products. The deoxyfluorination is highly selective for aldehydes over less electrophilic carbonyl substituents such as esters and amides (to form products **1j** and **1k**). This method was also effective for aldehydes derived from the biologically active molecules probenecid and adapalene (**1p** and **1q**).

Pyridine, quinoline, and isoquinoline carboxaldehydes were also good substrates for this transformation to form products **1r−1z**. In all cases, ^{19}F NMR spectroscopic analysis of the crude reaction mixtures showed high conversion and yield. In a few examples (e.g., **1r** and **1v**), the isolated yields were moderate due to the volatility of the difluoromethylpyridine products. Both electron-donating and electron-withdrawing substituents on the pyridine ring were well tolerated (for instance to form **1s** and **1t**). Halogen substituents on the pyridine were also generally compatible (see products **1u** and **1w**).

We next examined other classes of carbonyl substrates. Subjecting acetophenone and cyclohexanone to the standard

Scheme 1. Difluoromethylation of Benzaldehyde Substrates



[a]Conditions: (Chamber A) SDI (0.4 mmol, 2.0 equiv), KF (0.8 mmol, 4.0 equiv) in formic acid (0.4 mL); (Chamber B) aldehyde (0.2 mmol, 1.0 equiv), Me_4NF (0.8 mmol, 4.0 equiv) in DMF (1.0 mL) at room temperature for 4 h. Isolated yields average of two runs; yields in parentheses were determined by ^{19}F NMR spectroscopy using 4-fluoroanisole as the internal standard. [b]Performed using 5.0 mmol of aldehyde.

DOI: 10.1021/acs.orglett.9b00054
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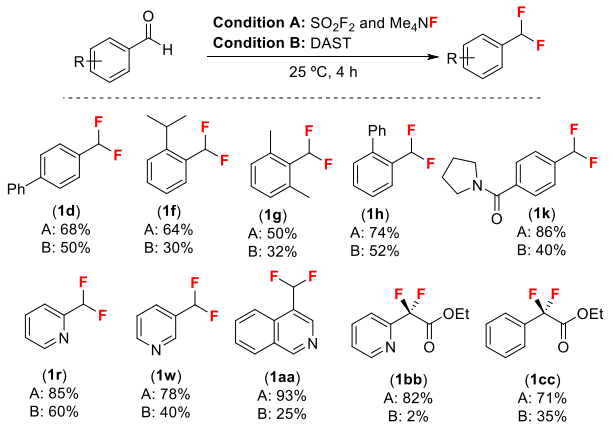
reaction conditions afforded decomposition of the ketone and no detectable quantity of the difluoromethylene-containing product. This is likely due to competitive enolate formation in the presence of Me_4NF. Benzophenone reacted to afford traces (<5%) of difluorodiphenylmethane. The low reactivity is likely due to the moderate electrophilicity of this substrate relative to the aldehydes. In contrast, more electrophilic α-keto ester derivatives proved to be excellent substrates for deoxyfluorination with SO_2F_2/Me_4NF. These reacted selectively to afford the α-*gem*-difluoro esters products **1aa** and **bb** in high yields. Notably, these motifs are commonly assembled via Cu-mediated cross-coupling,[19] and the deoxyfluorination approach provides a complementary route to accessing this functionality.[20]

A final set of studies focused on benchmarking this new method relative to DAST, the most common deoxyfluorinating reagent. All of the substrates in Scheme 1 were subjected to conditions reported as optimal for DAST, and the yield of the difluoromethyl product was assayed by ^{19}F NMR spectroscopy and compared directly to that achieved with SO_2F_2/Me_4NF (Scheme 2). The complete results are shown in Table S1. In

Scheme 2. Substrates That Afforded Significantly Higher Yields with SO_2F_2/Me_4NF Compared to DAST[a]



[a]**A**: (Chamber A) SDI (0.2 mmol, 2.0 equiv), KF (0.4 mmol, 4.0 equiv) in formic acid (0.2 mL); (Chamber B) aldehyde (0.1 mmol, 1.0 equiv), Me_4NF (0.4 mmol, 4.0 equiv) in DMF (0.5 mL) at room temperature for 4 h. **B**: aldehyde (0.1 mmol, 1.0 equiv), DAST (0.2 mmol, 2.0 equiv) in DCM (0.5 mL). For both conditions yields determined via ^{19}F NMR spectroscopy using 4-fluoroanisole as internal standard.

summary, the combination of SO_2F_2 and Me_4NF afforded a comparable or significantly higher yield than DAST in all cases examined. Representative examples are shown in Scheme 2, with an emphasis on substrates where SO_2F_2/Me_4NF was particularly effective. In general, SO_2F_2/Me_4NF performed especially well with substrates bearing *ortho*-substitution on the aromatic ring (e.g., **1f–h**), with pyridine- and quinoline-containing substrates (e.g., **1r**, **1v**, and **1z**), and with α-ketoester derivatives (e.g., **1aa** and **1bb**). Overall, these comparative studies demonstrate that for aldehyde and α-ketoester substrates the use of stable and inexpensive SO_2F_2/Me_4NF for carbonyl deoxyfluorination offers significant advantages in terms of product yields.

In summary, this Letter describes the development and scope of a method for carbonyl deoxyfluorination using sulfuryl fluoride and Me_4NF. This transformation provides access to difluoromethyl- and α-*gem*-difluoroester-substituted (hetero)-arene products under mild conditions. A direct comparison to DAST shows that SO_2F_2/Me_4NF affords comparable or significantly enhanced yield for a number of substrate classes. Ultimately, this feature, in combination with the relatively low cost and high stability of SO_2F_2/Me_4NF, renders this an attractive method for process-scale deoxyfluorination reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00054.

Procedure details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

DowAgrosciences is acknowledged for supporting this work.

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DOI: 10.1021/acs.orglett.9b00054
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