JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

A New Reagent for Direct Difluoromethylation

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Supporting Information

ABSTRACT: Molecular scaffolds containing alkylfluorine substituents are desired in many areas of chemical research from materials to pharmaceuticals. Herein, we report the invention of a new reagent ($Zn(SO_2CF_2H)_2$, DFMS) for the innate difluoromethylation of organic substrates via a radical process. This mild, operationally simple, chemoselective, and scalable difluoromethylation method is compatible with a range of nitrogen-containing heteroarene substrates of varying complexity as well as select classes of conjugated π-systems and thiols. Regiochemical comparisons suggest that the CF_2H radical generated from the new reagent possesses nucleophilic character.

The difluoromethyl group (CF_2H) is an intriguing structural motif that has great potential in the areas of pharmaceuticals, agrochemicals, and materials.[1−5] In the area of medicinal chemistry, the CF_2H unit is of special interest for its use in isostere-based drug design.[6] As a lipophilic hydrogen bond donor, CF_2H substitution offers an alternative to more traditional hydrogen bond donors while improving membrane permeability. For example, the difluoromethyl group has been utilized as a thiol mimic in the context of HCV NS3 protease inhibitors, successfully mimicking the cysteine CH_2SH P1 element in the parent compounds.[7] It has also been used as a hydroxamic acid hydroxyl isostere in a series of COX-2 and 5-LOX dual inhibitors, likely diminishing the metabolic toxicity expressed by some hydroxamic acids.[8] While several methods exist for the fluorination and alkylfluorination of organic substrates, strategies for direct difluoromethylation are less common, particularly in the context of heteroarene substrates. In this Communication, the invention of a reagent to accomplish the mild, direct, scalable, and predictably selective difluoromethylation of heteroarenes and related structures is reported.

Currently, all known methods for heteroarene difluoromethylation rely on prefunctionalization through a programmed approach (Figure 1A). Perhaps the most widely known strategy involves difluorination of aldehydes using (diethylamino)sulfur trifluoride (DAST).[9,10] Heteroarene−CF_2H compounds may also be accessed through a copper-catalyzed cross-coupling/decarboxylation sequence,[11] or via radical debromination from a heteroarene−CF_2Br precursor.[12] Although these methods boast impressive levels of reactivity and site selectivity, the need for methods achieving the direct transfer of the CF_2H unit has been explicitly voiced in a recent review.[13]

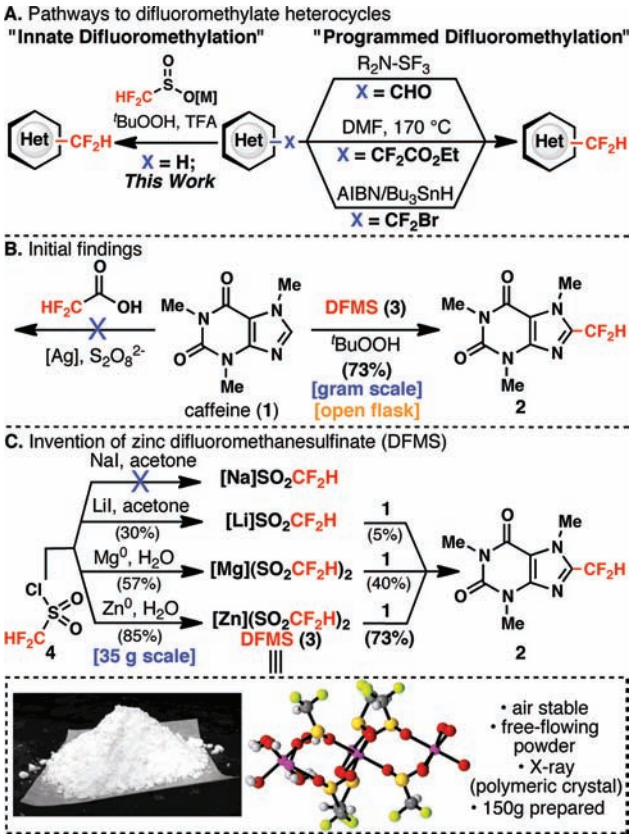


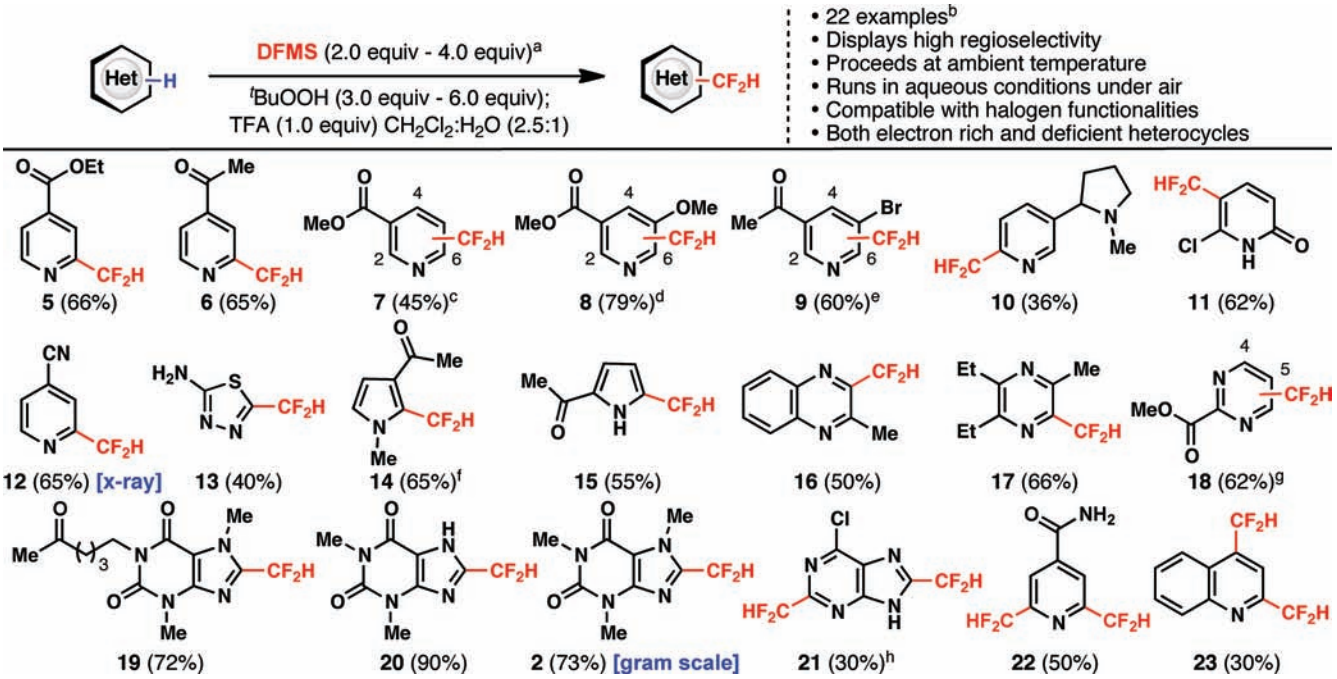
Figure 1. Invention of a new difluoromethylation reagent.

The pioneering work reported by Minisci on the decarboxylative generation of alkyl radicals and subsequent addition to heteroarenes (a form of innate[14] C−H functionalization) inspired initial forays into this area.[15] Thus, difluoroacetic acid was the first CF_2H source that was tested on caffeine (**1**) under a variety of oxidative conditions (Figure 1B). However, this strategy was unsuccessful, necessitating the exploration of alternative methods for generating CF_2H radicals. The only previous example of direct radical transfer of a CF_2H unit was reported by Chen and coworkers in the context of additions to olefins and alkynes (no other substrate classes reported) using non-commercial and operationally problematic HCF_2I gas as a precursor.[16]

Received: December 6, 2011
Published: January 9, 2012

dx.doi.org/10.1021/ja211422g | J. Am. Chem.Soc. 2012, 134, 1494−1497

Table 1. Scope of C−H Difluoromethylation of Heteroarene Substrates



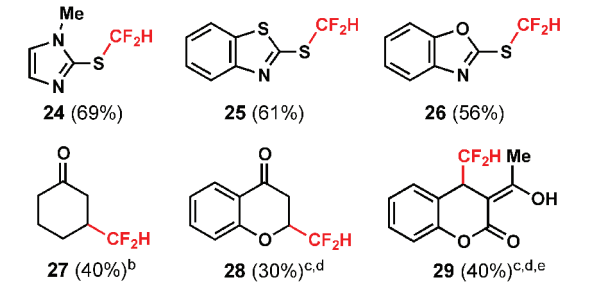
[a]Heterocycle (1.0 equiv), DFMS (2.0 equiv), *tert*-butyl hydroperoxide (3.0 equiv), TFA (1.0 equiv), 23 °C; isolated yields of chromatographically pure products are displayed, unless otherwise noted. [b]Both indole and 1-(2,4-dimethylfuran-3-yl)ethanone were unreactive, giving recovered starting material. [c]C2:C4:C6, 1.5:1.5:2. [d]C2:C4:C6, 1:1:2. [e]C2:C4:C6, 3:1:2. [f]Reaction showed incomplete conversion after 12 h, and a second addition of DFMS (2.0 equiv) and *tert*-butyl hydroperoxide (3.0 equiv) was done. [g]C4:C5, 4:1. [h]Heterocycle (1.0 equiv), DFMS (3.0 equiv), *tert*-butyl hydroperoxide (4.0 equiv), 23 °C.

In contrast, we have previously demonstrated the ease and practicality associated with the use of stable fluoroalkyl metal sulfinate complexes for the generation of trifluoromethyl radicals and subsequent addition to heteroarenes.[17] The seemingly simple extension of this approach to difluoromethylation was without precedent and required extensive experimentation.[18] Ultimately, after several strategies were evaluated, difluoromethanesulfonyl chloride was recognized as a convenient, commercially available starting point for the synthesis of a variety of different difluoromethylsulfinate reagents (Figure 1C). Using caffeine (**1**) as a model substrate, systematic variation of the metal counterion led to the identification of $Zn(SO_2CF_2H)_2$ (**3**, DFMS) as the optimum precursor for the CF_2H radical. DFMS is an easily prepared, air-stable, free-flowing white powder whose structure was confirmed by X-ray crystallographic analysis and shown to exist as a polymer in the solid state (see Supporting Information for more details).

With this new reagent in-hand, the scope of heteroarene difluoromethylation was evaluated on a broad cross-section of heterocyclic space. Many substrates showed good reactivity toward DFMS under the standard reaction conditions using *t*BuOOH in a CH_2Cl_2/H_2O solvent system, although select substrates suffered from poor conversion. In these cases, a second addition of DFMS and *t*BuOOH was added after 12−24 h to drive the reaction toward completion. It was also found that TFA showed improved rate and conversion for selected nitrogen heteroarene substrates, but was not essential to achieve the desired reactivity for most cases. Pyridines (**5**−**10**, **12**, **22**), pyrroles (**14**, **15**), pyrimidines (**18**), quinoxalines (**16**), pyrazines (**17**), xanthines (**2**, **19**, **20**), purines (**21**), quinoline (**23**), thiadiazoles (**13**), and pyridinones (**11**) are all competent participants in the described method, which is tolerant of several potentially sensitive functional groups.

In most cases, substrates with multiple potential reaction sites exhibit high levels of regioselectivity, commonly producing only one observable regioisomer with C−H functionalization occurring at electron-deficient positions.[17] It should be noted that all of the compounds illustrated in Table 1 are chemical entities with heretofore unreported synthetic procedures. In addition to the heteroarene substrates listed in Table 1, other organic substrates are also reactive toward difluoromethylation by the described process (Table 2). Aromatic thiols exhibit unexpected reactivity

Table 2. Difluoromethylation of Thiols and Enones[a]



[a]Standard conditions were followed, and yields were obtained after silica gel chromatography. [b]DFMS (1.0 equiv) and *tert*-butyl hydroperoxide (1.5 equiv) were used. [c]Second addition of DFMS (2.0 equiv) and *tert*-butyl hydroperoxide (3.0 equiv). [d]α,α,α-Trifluorotoluene was used instead of dichloromethane. [e]Keto:enol, 1:5.

toward the CF_2H radical, leading to the generation of difluoromethyl thioethers. Radical difluoromethylation was also successful in the context of other electron-deficient π-systems such as α,β-unsaturated enones.

dx.doi.org/10.1021/ja211422g | J. Am. Chem.Soc. 2012, 134, 1494−1497

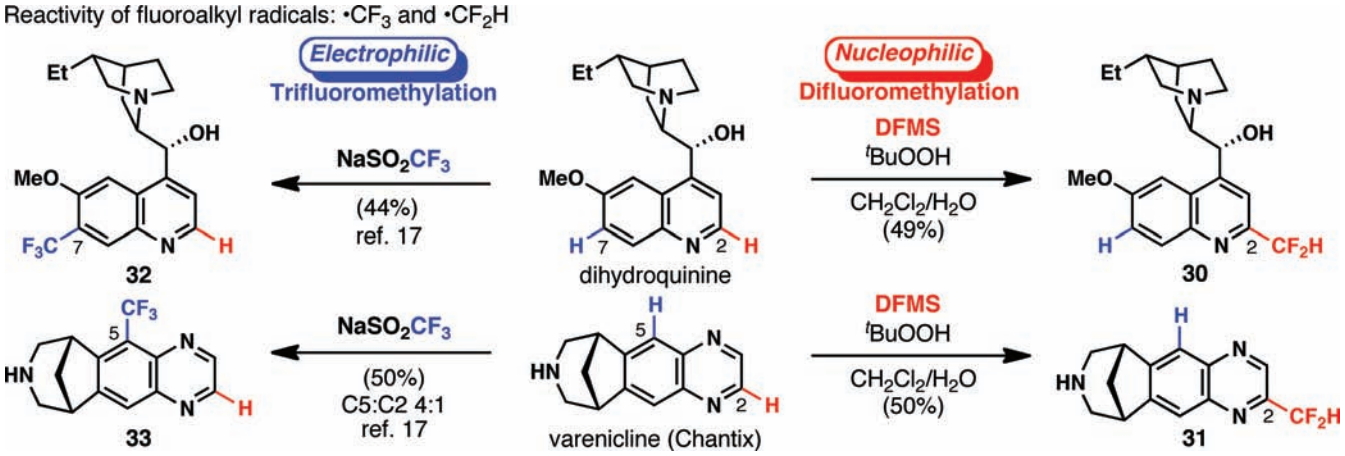


Figure 2. Regiochemical comparison of innate difluoro- and trifluoromethylations. Isolated yields after preparative HPLC purification.

In addition to the predictable site-selectivity observed in the difluoromethylation of simple small-molecule substrates, innate C−H difluoromethylation of complex reacting partners with many potential reactive sites is also predictable. As shown in Figure 2, the site-selectivity of difluoromethylation depends on the combined electronic properties of the reacting π-system and incoming radical species. This point is illustrated through a comparison between CF_3 and CF_2H radical additions to dihydroquinine and varenicline (marketed in the U.S. as the prescription medication Chantix by Pfizer). In both cases, high levels of selectivity are observed for CF_3 and CF_2H radical addition, in spite of the multiple potentially reactive sites. For both dihydroquinine and varenicline, innate radical C−H trifluoromethylation takes place at the most electron-rich position within the arene rings (C7 and C5, giving **32** and **33**, respectively).[17] Conversely, difluoromethylation occurs exclusively at electron-poor sites adjacent to heteroatoms within the heteroarene rings (both at C2, giving **30** and **31**). The orthogonality of these two approaches is a powerful example of the ability to fine-tune an approach to alkylfluorination when considering the innate reactivity and electronic nature of the two reacting components.

Although many substrates listed in Table 1 produce a single observable regioisomer, it is possible to access alternative substitution in some cases by judicious choice of organic solvent media. As shown in Figure 3, 4-acetylpyridine shows exceptional regioselectivity in CH_2Cl_2/H_2O, leading to exclusive formation of the C2-CF_2H product (**6-C2**). However, substituting DMSO for CH_2Cl_2 leads to significant reversal of regiochemistry, favoring the C3-CF_2H isomer (**6-C3**) in 1.5:1.0 ratio. Although C3 selectivity is modest under these conditions, the change in selectivity is significant considering that the C3-CF_2H product is inaccessible under standard reaction conditions.

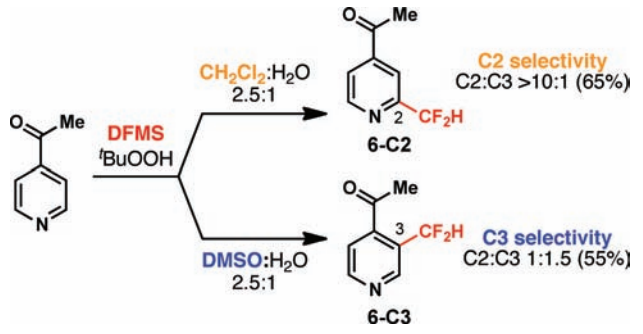


Figure 3. Solvent effects on regioselectivity. [a]Standard conditions were followed. [b]A second addition of DFMS (2.0 equiv) and *tert*-butyl hydroperoxide (3.0 equiv) was done.

In summary, a new reagent (DFMS, **3**) for direct difluoromethylation has been invented to access compounds of high value that, in almost all cases, were hitherto unknown. DFMS is effective for the direct transfer of a CF_2H unit to various organic substrates including heteroarenes, α,β-unsaturated enones, and aromatic thiols via user-friendly, scalable, open-flask conditions.[19,20] Changes in regioselectivity may be promoted by varying the organic cosolvent in the context of 4-substituted pyridines. Further examination of this and other mechanistic features is ongoing and will be reported in due course. DFMS has recently been commercialized by Sigma-Aldrich (product no. L510084).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical data for all new compounds, including ^1H, ^{13}C, and ^{19}F NMR and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

We are grateful to Prof. Arnold Rheingold and Dr. Curtis E. Moore for X-ray crystallographic analysis. Financial support for this work was provided by the NIH/NIGMS (GM-073949), the Uehara Memorial Foundation (postdoctoral fellowship for Y.F.), the NSF (predoctoral fellowship for R.A.R.), and Pfizer Inc. (postdoctoral fellowship for R.D.B.).

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(18) Attempts at synthesis of $NaSO_2CF_2H$ based on a previously reported method (Chen, Q.; Long, Z.; Faming, F.; Shuomingshu, S. G. China Patent CN 1221735 A 19990707, 1999) were fruitless. Synthesis of various $[M]SO_2CF_2H$ reagents from fluoroalkanesulfinic acid hydrazinium salts based on a previously reported method (Nanmyo, T.; Kashiwaba, T.; Morinaka, T.; Kawamoto, H.; Inoue, S.; Kume, T. PCT Int. Appl. 2010013687, 2010) was ineffective. Transferring CF_2H via reaction of fluorocarboxylic acids of the general structure [E.W.G.]$-CF_2-CO_2H$ analogous to a previously reported method (Forat, G.; Mas, J.-M.; Saint-James, L. U.S. Pat. Appl. 20020042542, 2002) was unsuccessful.
(19) A sample of DFMS left open to air on the benchtop retained its original purity and reactivity after two months.
(20) A provisional patent on this work has been filed, application no. 61565756.