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CF_2DSO_2Na: An Effective Precursor Reagent for Deuteriodifluoromethylthiolation and Deuteriodifluoromethylation

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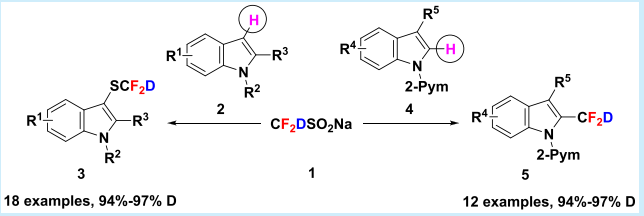
ABSTRACT: Deuteriodifluoromethythio (SCF_2D) and deuteriodifluoromethyl (CF_2D) are important functional groups in pharmaceutical and agrochemical compounds, and the introduction of these functional groups remains a challenging. We herein report a robust reagent for deuteriodifluoromethylthiolation and deuteriodifluoromethylation. Its potentials were successfully showcased by deuteriodifluoromethylation and deuteriodifluoromethylthiolation of indoles with high-level deuterium incorporation. The reagent also has potential for deuteriodifluoromethylation and deuteriodifluoromethylthiolation of wide range of other natural or synthetic bioactive molecules.



Compared with the C−H bond, the C−D bond needs more bond dissociation energy to be unlinked. Thus replacing the C−H bond with the C−D bond greatly enhances the properties, including the metabolism and pharmacokinetics, while preserving the performance and selectivity of the drug molecule. Deuterium-labeling methods have been extensively applied in mechanistic studies, organic synthesis, drug metabolism analysis, and structure determination.[1] In 2017, deutetrabenazine was authorized by the U.S. Food and Drug Administration (FDA) for the treatment of tardive dyskinesia and Huntington's disease (Figure 1a).[2]

The modification of fluorine or fluorine-containing functional groups into bioactive molecules can significantly optimize their lipophilicity, metabolic stability, and bioavailability.[3] In particular, the difluoromethylthio group (SCF_2H) and the difluoromethyl group (CF_2H) are superior fluoro-containing groups for this purpose. They are lipophilic hydrogen-bond donors and can be used as biological isosteres with high metabolic stability toward biological thiols, amines, and alcohols.[4] Interestingly, the simultaneous incorporation of both deuterium and fluorine atoms into a bioactive molecule has rarely been reported. We envisage that this could be a general method for drug development, and $-SCF_2D$/$-CF_2D$ are two very attractive yet challenging functional groups. To our knowledge, no effective precursor reagent has been developed for this transformation.

A review of the literature reveals that there are few methods to introduce CF_2D and SCF_2D into molecules directly, and these functional groups are still challenging functional groups because of the unavailability of precursor reagents and the difficult deuterium incorporation. The two "CF_2D" reagents were derived from trifluoromethylation reagents, replacing one fluorine atom with a deuterium atom. Typically, trimethyl(deuterofluoromethyl)silane derived from the Ruppert−Prakash reagent is the most recognizable example; however, this reagent was also reported to transfer a deuterium atom instead of the "CF_2D" group.[5] Sulfoximine, is another reagent, but the deuterium binding level of the "CF_2D" group of the reagent is too low to be used.[6] Nevertheless, there is only one exception of 19-deutero-19,19-difluoroandrost-4-3,17-dione synthesis to explore the mechanism of aromatase inactivation.[7] Therefore, there is a need for an efficient reagent for introducing "CF_2D/SCF_2D" (Figure 1b). In 2016, Billard's group successfully synthesized the molecule with SCF_2D through a two-step synthesis (Figure 1c).[8] In 2020, Yi's group reported a mild and transition-metal-free method for the one-pot preparation of deuterated difluoromethyl thioethers in high yield with a high deuterium incorporation level (Figure 1d).[9] Colby's group synthesized ketones and sulfones with CF_2D by releasing trifluoroacetate from highly fluorinated gem glycol (Figure 1e).[10] In 2020, Jamison's group reported the use of the continuous-flow method to produce deuteriodifluoromethylated products by reacting chlorodifluoromethane gas with aldehydes in high yields with a high deuterium incorporation level (Figure 1f).[11] Recently, Yan's group reported the hydrogen−deuterium (H/D) exchange reaction of difluoromethylarenes in DMSO-d_6 solution by *t*-BuOK catalysis (Figure 1g).[12] Given the superior metabolic stability of the C−

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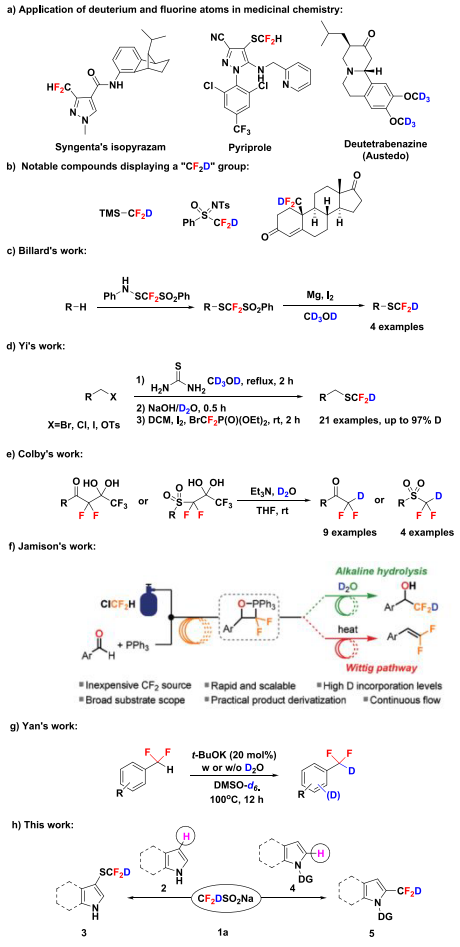
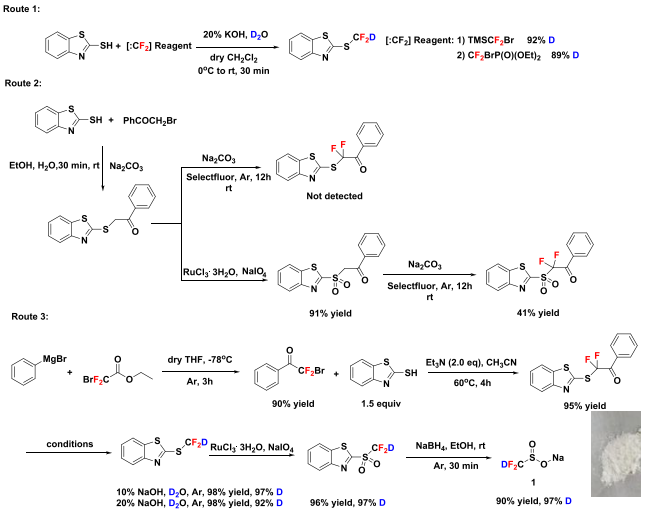


Figure 1. (a) Examples of deuterated drugs and fluorine-containing drugs. (b) Notable compounds displaying a "CF_2D" group. (c) Billard's work. (d) Yi's work. (e) Colby's work. (f) Jamison's work. (g) Yan's work. (h) This work.

D bond, CF_2D- and SCF_2D-containing compounds have potential for drug discovery. We aim to synthesize building blocks for introducing CF_2D and SCF_2D groups and further showcase their potential in modifying bioactive molecules of natural or synthetic origins.

CF_2HSO_2Na is a useful reagent for difluoromethylation and difluoromethylthiolation.[13−23] Therefore, we hypothesize that replacing the hydrogen atom of the reagent with a deuterium could be a viable approach to develop reagents for the introduction of CF_2D and SCF_2D groups into heterocyclic molecules. The starting material for the preparation of CF_2DSO_2Na is $BTSCF_2D$. First, we adopted the method of Hu's group by using difluorocarbene reagent to react with 2-benzothiazolyl mercaptan in deuterium aqueous solution containing 20% KOH (weight percentage). The deuteration rate of $TMSCF_2Br$ was 92%, and that of $CF_2BrP(O)(OEt)_2$ was 89% (Scheme 1, route 1).[24] Presumably, the hydrogen on mercaptan affects the deuterium incorporation of the product; therefore, bromoketone was instead used first followed by fluorination and benzoyl removal to introduce deuteration (Scheme 1, route 2). The result shows that the fluorination step was difficult. A limited yield of 41% was achieved by using 2.5 equiv of Selectfluor. Then, we changed the sequence and did the fluorination first, followed by a substitution (Scheme 1, route 3). This time, the desired deuterated sodium

Scheme 1. Methods for the Preparation of CF_2DSO_2Na (1)



difluoromethylsulfinate (CF_2DSO_2Na) was obtained in a high overall yield of 72% (for a total of five steps) with a high level of deuterium incorporation (97% D). It is a white powder that is insensitive to light but prone to moisture.

With this novel reagent in hand and considering that indole is a common structure in medicines and natural products, we reacted it with various electron-rich aromatics, for example, indoles, and checked if Friedel−Crafts-type deuteriodifluoromethylation could occur. It was observed that the reaction of indole with reagent **1** under the presence of 2.0 equiv of TMSCl and 3.0 equiv of $(EtO)_2P(O)H$ proceeded smoothly to afford product **3a** in a 87% yield with 95% deuterium incorporation. Likewise, different indoles were screened for the deuteriodifluoromethylthiolation reaction to investigate the reaction scope. As illustrated in Scheme 2, indoles with multifarious functional groups such as methyl (**3b**, **3l**), methoxy (**3c**, **3i**, **3k**), alkoxy (**3h**, **3j**), halogen (**3f**), ester (**3e**), trifluoromethyl (**3g**), and formyl (**3d**) groups were compatible with this reagent and furnished the corresponding products in moderate to high yields (49−91%) with high levels of deuterium incorporation (94−96%). The reaction of multisubstituted indoles (**3m−o**) also formed the corresponding deuteriodifluoromethylthiolation compounds in high yield (79−92%) with a high level of deuterium incorporation. In general, indoles equipped with electron-donating groups have higher yields than those with electron-withdrawing groups. *N*-Substituted indoles (**3p**, **3q**) also reacted to obtain the desired product in 91 and 64% yield with high levels of deuterium incorporation under the conditions. Remarkably, 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolone was also compatible with the reaction conditions, giving the product **3r** in a moderate yield (75%) with high levels of deuterium incorporation (95%). Meanwhile, we also carried out a gram-scale reaction that gave product **3a** in a high yield of 82%, and the level of deuterium incorporation did not change.

Inspired by the successful introduction of the deuteriodifluoromethylthiol group at the C-3 position of *N*-pyrimidyl indoles, we next set our sights on the scope of different indole motifs during the process of this direct C-2 deuteriodifluoromethylation. As presented in Scheme 3, different positions of the *N*-pyrimidine indoles can undergo deuteriodifluoromethylation at the C-2 position. It is noteworthy that this transformation was proved to be dramatically compatible

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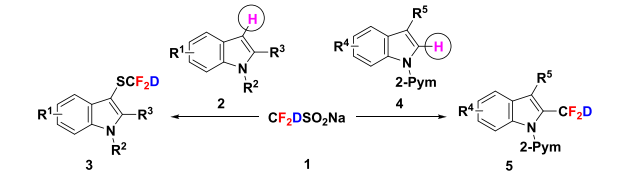
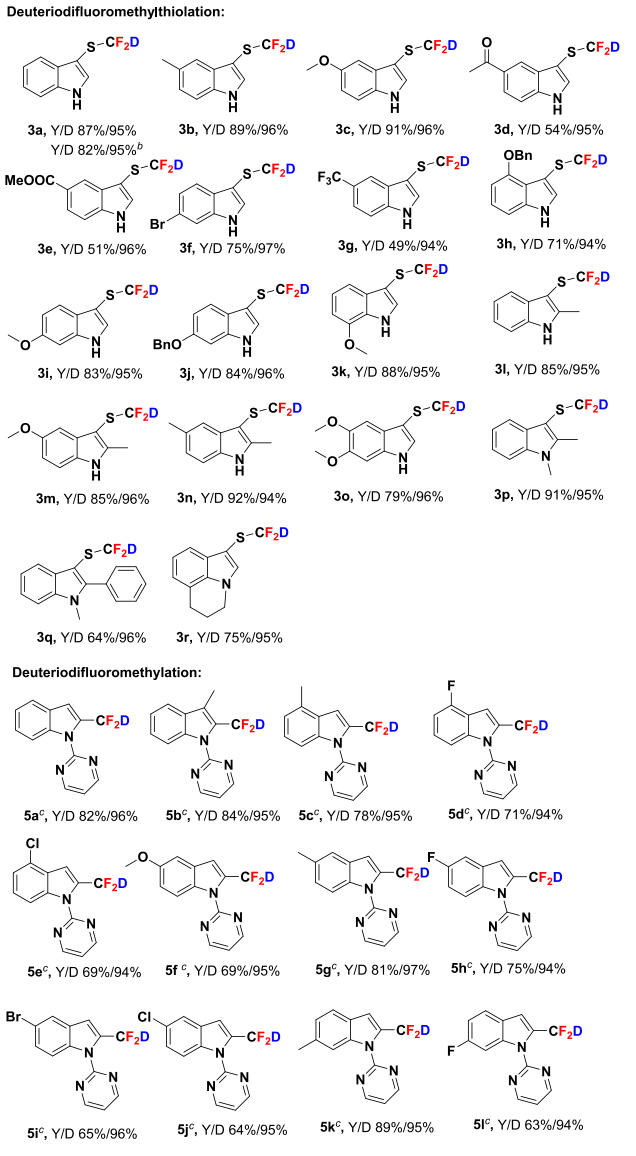
Scheme 2. Deuteriodifluoromethylthiolation and Deuteriodifluoromethylation of Indoles[a]



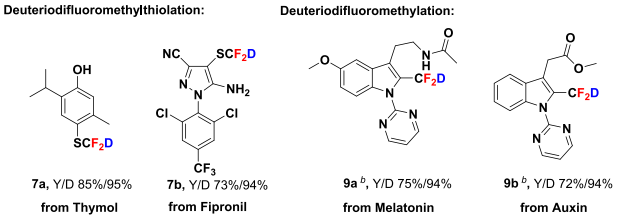


[a]Reaction conditions: **2** (0.4 mmol), **1** (0.2 mmol), $(EtO)_2P(O)H$ (0.6 mmol), TMSCl (0.4 mmol), toluene (1 mL), 85 °C, 3 h. Isolated yields. [b]5 mmol scale. [c]Reaction conditions: **4** (0.3 mmol), **1** (0.2 mmol), $CuCl_2$ (10 mol %), $K_2S_2O_8$ (0.6 mmol), CH_3CN (2 mL), 50 °C, 36 h, under air. Isolated yields.

with the indole **4a**, providing the desired product **5a** in 82% yield. Additionally, the substituted indoles of C-3, C-4, C-5, and C-6 likewise reacted well. Among them, C-2 deuteriodifluoromethylation products were smoothly gained in moderate to good yields (**5b**–**l**).

Finally, we tried to introduce deuteriodifluoromethylation and deuteriodifluoromethylthiolation into pharmaceutical molecules and natural products. By using the CF_2DSO_2Na/PPh_2Cl/Me_3SiCl system, thymol (**6a**) generated the corresponding SCF_2D product **7a** in satisfactory yields with 95% deuterium incorporation. The pesticide fipronil **6b** furnished the SCF_2D product **7b** in 73% yield with 94% deuterium incorporation. In addition, the direct deuteriodifluoromethylation of drug molecules and natural products, such as melatonin (**8a**) and auxin (**8b**), can react smoothly under the standard conditions, and the corresponding products **9a** and **9b** were obtained in good yields with high levels of deuterium incorporation (94%).

Scheme 3. Late-Stage Deuteriodifluoromethylation and Deuteriodifluoromethylthiolation of Drugs and Natural Products[a]



[a]Reaction conditions: **6a** and **6b** (0.2 mmol), CF_2DSO_2Na (0.8 mmol), Ph_2PCl (0.8 mmol), Me_3SiCl (0.3 mmol), 90 °C, CH_3CN (2 mL), under Ar, 12 h. Isolated yields. [b]Reaction conditions: **8a** and **8b** (0.2 mmol), CF_2DSO_2Na (0.3 mmol), $CuCl_2$ (10 mol %), $K_2S_2O_8$ (0.6 mmol), CH_3CN (2 mL), 50 °C, 36 h, under air. Isolated yields.

In summary, we developed an effective precursor reagent for deuteriodifluoromethylthiolation and first deuteriodifluoromethylation. This reagent achieved deuteriodifluoromethylation and deuteriodifluoromethylthiolation at the C-2 and C-3 positions of indoles, with a high deuteration incorporation. This reagent can be used to introduce SCF_2D and CF_2D to drug molecules and natural products, providing a unique and powerful strategy for drug discovery and modification.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01882.

Spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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