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Nucleophilic Iododifluoromethylation of Carbonyl Compounds Using Difluoromethyl 2-Pyridyl Sulfone

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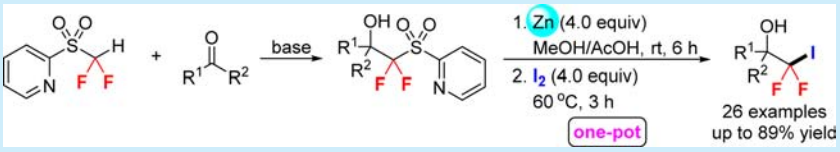
Supporting Information

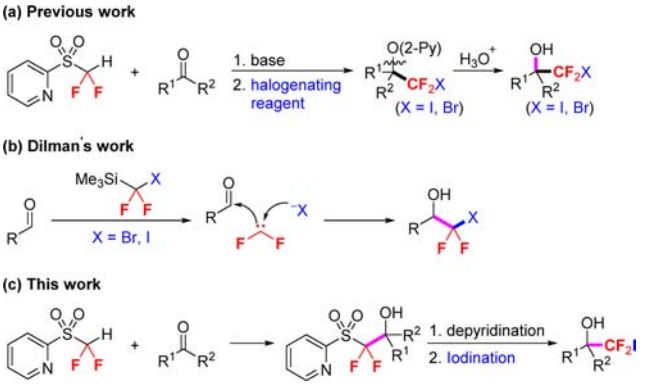


ABSTRACT: A new, efficient method for iododifluoromethylation of carbonyl compounds utilizing difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$) is described. This transformation is achieved by a nucleophilic addition of 2-$PySO_2CF_2H$ with carbonyl compounds and a subsequent iodination of sulfinate, which is generated in situ by a novel zinc-mediated depyridination reaction. The method employs mild reaction conditions, exhibits excellent functional-group tolerance, and can be used in the synthesis of various iododifluoromethylated carbinols.

Organofluorine compounds play significant roles in the fields of pharmaceuticals, agrochemicals, and materials.[1] It is well established that selective introduction of fluorinated moieties into organic molecules can often lead to profound effects on the lipophilicity and metabolic stability of organic molecules compared to their nonfluorinated counterparts.[2] Among various fluorine-containing fragments, the iododifluoromethyl group ($-CF_2I$) is an intriguing structural motif with great potential, which can be exploited for the synthesis of various difluoromethylenated products,[3] as well as candidates for investigating halogen bonding used in crystal engineering.[4] Consequently, these applications have stimulated researchers to develop efficient methods for incorporation of the CF_2I group into organic molecules under mild conditions. Existing methods for the synthesis of compounds with the CF_2I group mainly involve modifications of CF_2I-containing substances[5] or iodination of the difluoromethylene-containing molecules.[6] However, the synthesis of iododifluoromethylated carbinols is less studied because they are still challenging to access.[7]

In 2012, utilizing difluoromethyl 2-pyridyl sulfone (**1**, 2-$PySO_2CF_2H$) as a nucleophilic fluoroalkylation reagent, our group had achieved a formal nucleophilic iododifluoromethylation of carbonyl compounds via halogenation of the Julia–Kocienski intermediates and subsequent deprotection (Scheme 1a).[7] Recently, Dilman and co-workers reported a method for direct nucleophilic iododifluoromethylation of aldehydes using Me_3SiCF_2X (X = I or Br), which is based on the generation of a transient halodifluoromethyl carbanion from difluorocarbene and a halide anion (Scheme 1b).[8] Although the products were obtained in excellent yields, the scope of this method is limited to nonenolizable aldehydes. Enolizable aldehydes are not suitable substrates because difluorocarbene, generated from Me_3SiCF_2X (X = I or Br), readily undergoes a [2 + 1] cycloaddition with the enol form of aldehydes.[9]

Scheme 1. Strategies for Preparation of Iododifluoromethylated Carbinols



Furthermore, direct iododifluoromethylation of ketones with Me_3SiCF_2X (X = I or Br) has not been achieved, probably as a result of their lower electrophilicity. In our previous protocol, 2-$PySO_2CF_2H$ and carbonyl compounds condense in the presence of a base to afford an adduct, which quickly undergoes Smiles rearrangement, giving the difluoromethylene-containing sulfinate.[7,10] Iodo- and bromodifluoromethylated products were obtained by halogenating the sulfinate intermediate, followed by deprotection (Scheme 1a). Further investigation indicates that the removal of the pyridinoxyl group proceeds through a carbenium intermediate, and therefore, it is difficult to remove the pyridioxyl group on the substrates bearing electron-withdrawing substituents.[11] Moreover, this method is not compatible with the aliphatic system,[11] where multiple reaction

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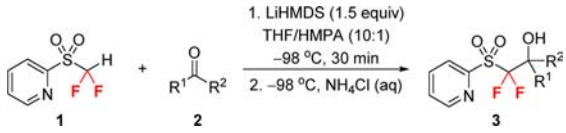
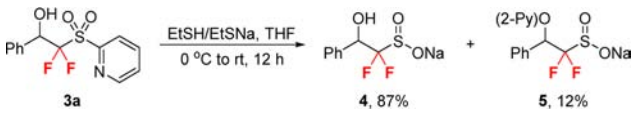
pathways from the carbenium ion intermediate, such as rearrangement and elimination, are possible. We were also aware that Smiles rearrangement is sensitive to the steric hindrance of the substrate such that the formation of sulfinate intermediate is not efficient with diaryl ketones.[12] To address these problems, we herein report a new approach to achieve nucleophilic iododifluoromethylation of carbonyl compounds with 2-PySO_2CF_2H (Scheme 1c). In this strategy, Smiles rearrangement is avoided, and we have developed an efficient zinc-mediated depyridination reaction for the preparation of sulfinate intermediates.

In the nucleophilic addition reaction between 2-PySO_2CF_2H and carbonyl compounds, it was found that the S−O Smiles rearrangement of the alcoholate anions took place readily. We speculated that the Smiles rearrangement could be hampered by decreasing both the reaction temperature and the polarity of the solvent. Our research commenced with the nucleophilic addition of 2-PySO_2CF_2H **1** to carbonyl compounds **2**, according to the previous report.[12] We modified the reaction conditions, and the products **3** were obtained in good to excellent yields (Scheme 2; for details, see Supporting Information (SI)). With a series of the (2-pyridylsulfonyl)-difluoromethylated carbinols **3** in hand, converting diverse (2-pyridylsulfonyl)difluoromethylated carbinols **3** to the corresponding sulfinates became a key step to achieve our goal. In recent years, several methods have been developed for the efficient synthesis of fluoroalkanesulfinates by removing the heteroaryl group in fluoroalkyl heteroaryl sulfones.[13] We tested **3a** using the EtSNa/EtSH system,[13a] and product **4** was formed in 87% yield, while the S−O Smiles rearrangement byproduct **5** was obtained in 12% yield (Scheme 3); this side reaction could not be eliminated. Furthermore, this method is not operationally and environmentally friendly because EtSH has a strongly disagreeable odor. The formation of **5** indicates that **3a** is readily deprotonated under basic conditions, which results in the undesired S−O Smiles rearrangement.

Scheme 2. Nucleophilic Addition of (2-Py)SO_2CF_2H to Carbonyls

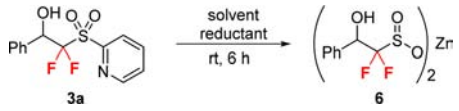


Scheme 3. Preparation of Difluoroalkylsulfonates from 3a



Given these disadvantages, we set out to develop a new and efficient method to prepare fluorinated sulfinates. Inspired by a preparation of sulfinates through a reduction of the electron-withdrawing heterocyclic sulfone by treatment with Zn/EtOH−AcOH,[14] we attempted to conduct the preparation of fluorinated sulfinates under similar reaction conditions. With **3a** as a model compound, the desired fluorinated sulfinate **6** was obtained in 90% yield through the depyridination using a large excess of Zn in DMSO/AcOH (Table 1, entry 1). We found that the depyridination proceeded smoothly to give sulfinate **6**

Table 1. Survey of Reaction Conditions for Synthesis of Sulfinate 6 by Reductive Depyridination[a]

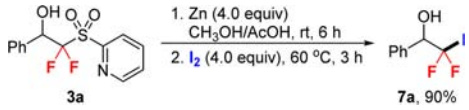


entry	solvent	reductant (equiv)	**6**, yield (%)[b]
1	DMSO/AcOH (5:1)	Zn (15.0)	90
2	MeOH/AcOH (10:1)	Zn (4.0)	95
3	AcOH	Zn (4.0)	85
4	MeOH	Zn (4.0)	0
5	MeOH/AcOH (10:1)	–	0
6	MeOH/AcOH (10:1)	Mg (4.0)	trace
7	MeOH/AcOH (10:1)	Fe (4.0)	0

[a]Reaction conditions: **3a** (0.3 mmol, 1.0 equiv), solvent (3.0 mL), rt, 6 h. [b]Yields were determined by ^{19}F NMR.

in 95% yield when 4.0 equiv of Zn was used in CH_3OH/AcOH (entry 2). Control experiments demonstrated that the depyridination required both AcOH and Zn (entries 3−5), and in the absence of any of these components, the conversion into the desired sulfinate was not observed. In addition, magnesium and iron metal were found to be ineffective (entries 6−7). The in situ generated sulfinate underwent iodination by treatment of I_2 at 60 °C, affording the corresponding product **7a** in 90% yield (Scheme 4).

Scheme 4. One-Pot Synthesis of Iododifluoromethylated Carbinols 7a from 3a



Having established an efficient route to **7a**, we assessed the scope of the method with regard to the carbonyl compounds (Scheme 5). This reaction exhibits a broad substrate scope. In addition to benzaldehyde (**7a**) and 2-naphthaldehyde (**7b**), aromatic aldehydes containing the electron-donating (**7c**, **7d**) and electron-withdrawing substituents (**7e**−**7i**) were well tolerated. Various functional groups, such as methoxyl, dimethylamino, cyanide, trifluoromethyl, bromide, chloride, and ester, were found to be compatible with the reaction conditions. The structure of **7e** was confirmed by X-ray crystal structure analysis (see SI).[15] Beyond phenyl derivatives, heterocyclic substrates such as benzothiophene work equally well (**7j**). Aliphatic aldehydes with acidic α-protons gave iododifluoromethylation product **7k** in 47% yield. Cinnamaldehyde afforded product **7l** in good yield. It is noteworthy that ketones are also suitable substrates, while, in Dilman's recent work, nucleophilic iododifluoromethylation of carbonyl compounds was only limited to aldehydes. Aromatic ketones such as acetophenone (**7m**, **7n**), acetothienone (**7o**), and some other substituted aromatic ketones (**7p**, **7q**) could be employed with our method. Aromatic ketones bearing a C=C double bond (**7r**) and C≡C triple bond (**7s**) were also amenable to this reaction. It is noteworthy that sterically hindered ketones, such as benzophenone, were also reactive, providing product **7t** in satisfactory yield. Additionally, when aliphatic ketones were used as substrates (**7u**−**7w**), the iododifluoromethylation products were obtained in good yields.

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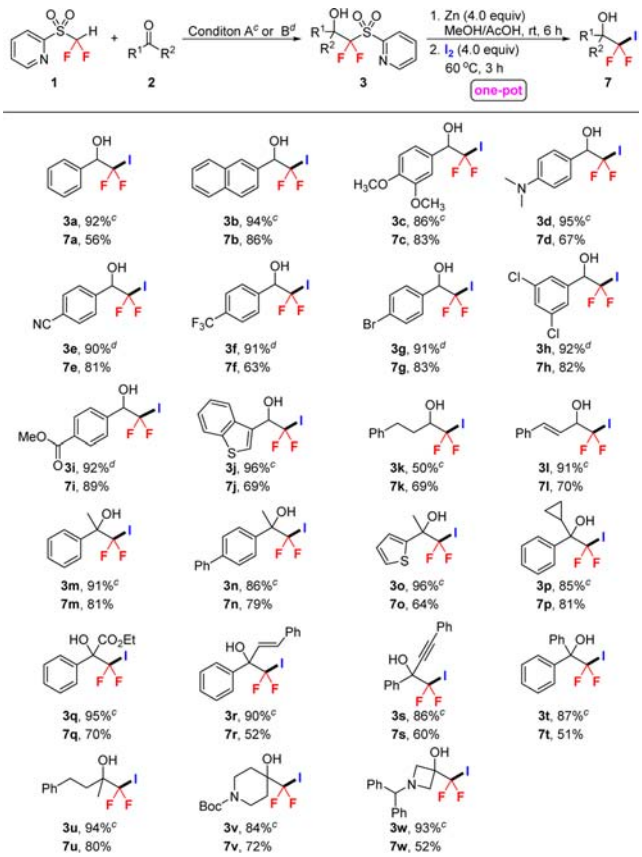
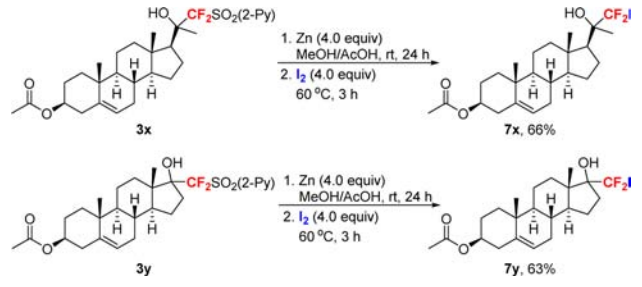
Scheme 5. Iododifluoromethylation of Various Carbonyl Compounds 2[a,b]



[a]Reaction conditions: **3** (1.0 mmol, 1.0 equiv), Zn (4.0 equiv), I_2 (4.0 equiv), MeOH (4.0 mL), AcOH (0.4 mL). [b]Isolated yield. [c]Condition A: LiHMDS (1.5 equiv), THF/HMPA (10:1), −98 °C, 0.5 h. [d]Condition B: *t*-BuOK (1.5 equiv), THF, −78 °C, 0.5 h.

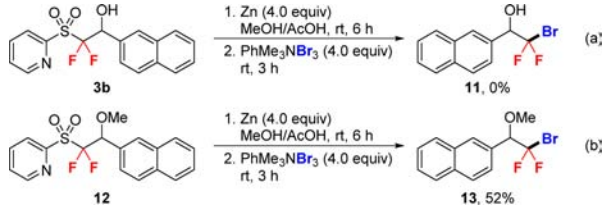
As a demonstration of the importance of this protocol, in addition to the simple molecules, we applied this strategy to complex molecules. As shown in Scheme 6, the (2-pyridyl-sulfonyl)difluoromethylated carbinols **3x** and **3y** could be achieved from steroids in excellent yields. It should be mentioned that the depyridination reactions of carbinols **3x** and **3y** proceeded slowly, and a longer reaction time was needed. By a combination of depyridination and iodination, products **7x** and **7y** were prepared in one pot in 66% and 63% yield, respectively (Scheme 6). In 2014, a method for direct halodifluoromethylation of iminium ions with Me_3SiCF_2Br has been described by Dilman's group,[16] but halodifluoromethylation of imines has not been reported to date. We sought to apply our method to furnish iododifluoromethylated imines. Compound **9** participated in the removal of the pyridyl group by reduction, and subsequent iodination afforded the amine **10** in 76% yield (Scheme 7). Bromodifluoromethylated carbinols were also evaluated according to a one-pot procedure, whereas no product **11** was detected (Scheme 8a). Nevertheless, when the hydroxyl was protected, bromodifluoromethylated product **13** was achieved in 52% yield (Scheme 8b).

Scheme 6. Iododifluoromethylation of 3x and 3y



Scheme 7. Nucleophilic Iododifluoromethylation of Imine

Scheme 8. Bromodifluoromethylation of Carbonyl Compounds



In conclusion, we have developed an efficient method for nucleophilic iododifluoromethylation of aldehydes and ketones using 2-$PySO_2CF_2H$. In this synthetic strategy, nucleophilic addition of 2-$PySO_2CF_2H$ with carbonyl compounds has been achieved and the use of a Smiles rearrangement to produce a sulfinate intermediate is avoided. A novel zinc-mediated depyridination reaction for the preparation of sulfinate is reported. The method is mild and tolerant of a variety of functional groups. It thus serves as a new approach to prepare diverse iododifluoromethylated carbinols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01258.

Experimental procedures and characterization data for products (PDF)

Crystallographic data for compounds **7e** (CIF)

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Notes

The authors declare no competing financial interest.

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