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Fluorinated Sulfonates

From Difluoromethyl 2-Pyridyl Sulfone to Difluorinated Sulfonates: A Protocol for Nucleophilic Difluoro(sulfonato)methylation**

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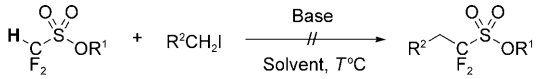
Fluorine, characterized by its small size and high electronegativity, often furnishes organic molecules with unequalled chemical and biological properties including stability, lipophilicity, and bioavailability.[1] The sulfonic acid functional group has not only found its use in modern materials such as proton-exchange membranes and surfactants,[2] but also in synthetic molecules with important biological and pharmacological activities such as antiulcer, antibacterial, antipseudomonal, and squalene synthase inhibition activities.[3] Based on this scenario, α,α-difluorinated sulfonate derivatives, as an important subclass of lightly fluorinated compounds, are of great interest in life and materials sciences. Furthermore, owing to the isopolar and isosteric characters of the difluoromethylene group to an oxygen atom, difluorinated sulfonates can be exploited to replace the labile sulfate esters.[1d] Although α,α-difluorinated phosphonic acids have been used to inhibit and probe enzymes and proteins that bind or hydrolyze phosphate for many years, only in recent years, attention has been paid on α,α-difluorinated sulfonates to design effective sulfatase inhibitors.[4,6] Moreover, in relation with the perfluorinated sulfonic acids and their derivatives, the performance of these difluorinated counterparts are also of great interest in materials science owing to their acidity and facile biodegradability.[5] Thus, many α,α-difluorinated sulfonates have been synthesised using different protocols, including the electrophilic fluorination of the sulfonates,[4c,6] dehalosulfination or -sulfonation of α,α-difluoroalkyl halides,[7a–c] sulfonation of 1,1-difluoroalkenes,[7d] sulfination of α,α-difluorosilanes,[7e] and fluorinated sultone rearrangements.[7f] Apparently, one of the disadvantages of these protocols is that the fluorine atoms and sulfonato group have to be incorporated sequentially.

Based on nucleophilic fluoroalkylation,[8] one can envision a nucleophilc difluoro(sulfonato)methylation pathway for the direct introduction of difluoro(sulfonato)methyl group into organic frameworks. Indeed, Li and Liu had reported a nucleophilic introduction of a difluoromethylene sulfonamide group ($-CF_2SO_2NR_2$) into aromatic aldehydes.[9] However, these synthons are not ideal for the introduction of the sulfonic acid functional group owing to the sluggish hydrolysis rates of the sulfonamides. Our initial attempts towards this goal involved treating difluoromethanesulfonates (as pronucleophiles) and alkyl iodides (as electrophiles) under basic conditions. These attempts failed as a result of the instability and low reactivity of difluoromethanesulfonates anions (Scheme 1, for details, see the Supporting Information), thus implying that there are some challenges in the nucleophilic difluoro(sulfonato)methylation reaction.



Scheme 1. Attempted nucleophilic difluoro(sulfonato)methylation reaction of alkyl iodides with difluoromethanesulfonates.

It is well known that alkyl sulfonyl-substituted heteroaromatic compounds can readily undergo *ipso*-substitution reaction with nucleophiles, thus giving the corresponding heteroaromatics and alkyl sulfinates.[10] However, to the best of our knowledge, there has been no report on the synthetic utility of heteroaryl sulfones as sulfinate or sulfonate equivalents in the nucleophilic (sulfonato)methylation reactions.[11] Herein, we disclose a new synthetic application of difluoromethyl sulfones as a difluoro(sulfonato)methyl equivalent ($-CF_2SO_3^-$), which enables a unique synthesis of α,α-difluoroalkyl sulfonates from primary alkyl halides and primary alcohol triflates (Scheme 2).

To realize this nucleophilic substitution, the reaction between difluoromethyl heteroaryl or electron-deficient aryl sulfones and alkyl halides or sulfonates were examined with extensive screening of the reaction conditions (Table 1). Surprisingly, by applying the reported optimal reaction conditions for the nucleophilic substitution of difluoromethyl phenyl sulfone with alkyl iodides,[12] only difluoromethyl 2-pyridyl sulfone **1b** gave a detectable amount of substituted product (Table 1, entries 1–4). In all cases, the decomposition of the difluoromethyl sulfones was observed as the predominant outcome. The preliminary results showed that these aryl substituents were less effective for the stabilization of difluoromethyl anions in comparison with the phenyl group. To suppress the decomposition of the anion species, the

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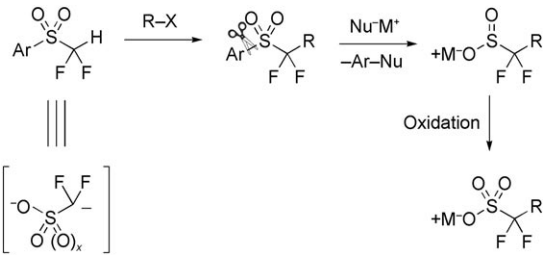
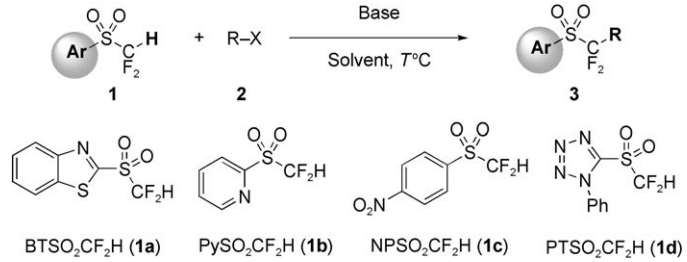


Scheme 2. Nucleophilic difluoro(sulfonato)methylation reaction with difluoromethyl sulfones.

Table 1: Screening of reagents and optimization of reaction conditions.



Entry	Sulfone (equiv)	Base (equiv)	Halide (equiv)	Solvent[a]	T [°C]	Yield [%][b]
1	**1a** (1.0)	*t*BuOK (2.0)	*n*-$C_7H_{15}I$ (4.0)	DMF	−45	0
2	**1b** (1.0)	*t*BuOK (2.0)	*n*-$C_7H_{15}I$ (4.0)	DMF	−45	10
3	**1c** (1.0)	*t*BuOK (2.0)	*n*-$C_7H_{15}I$ (4.0)	DMF	−45	0
4	**1d** (1.0)	*t*BuOK (2.0)	*n*-$C_7H_{15}I$ (4.0)	DMF	−45	0
5	**1b** (1.0)	LiHMDS (2.0)	*n*-$C_7H_{15}I$ (4.0)	THF	−78	0
6	**1b** (1.0)	LiHMDS (2.0)	*n*-$C_7H_{15}I$ (4.0)	THF/HMPA	−78	45
7	**1b** (1.0)	LiHMDS (2.0)	*n*-$C_7H_{15}I$ (4.0)	THF/HMPA	−98	88
8	**1b** (1.0)	LiHMDS (2.0)	*n*-$C_7H_{15}I$ (4.0)	Et_2O/HMPA	−98	57
9	**1b** (2.0)	LiHMDS (2.0)	*n*-$C_7H_{15}I$ (1.0)	THF/HMPA	−98	80
10	**1b** (1.3)	LiHMDS (1.5)	*n*-$C_7H_{15}I$ (1.0)	THF/HMPA	−98	79
11	**1b** (1.3)	NaHMDS (1.5)	*n*-$C_7H_{15}I$ (1.0)	THF/HMPA	−98	0
12	**1b** (1.3)	KHMDS (1.5)	*n*-$C_7H_{15}I$ (1.0)	THF/HMPA	−98	0
13	**1a** (1.0)	LiHMDS (2.0)	*n*-$C_7H_{15}I$ (1.0)	THF/HMPA	−98	0
14	**1c** (1.0)	LiHMDS (2.0)	*n*-$C_7H_{15}I$ (1.0)	THF/HMPA	−98	0
15	**1d** (1.0)	LiHMDS (2.0)	*n*-$C_7H_{15}I$ (1.0)	THF/HMPA	−98	0
16	**1d** (1.0)	LiHMDS (2.0)	*n*-$C_5H_{11}Br$ (4.0)	THF/HMPA	−98	37
17	**1b** (1.3)	LiHMDS (1.5)	*n*-C_4H_9OTs (1.0)	THF/HMPA	−98	0
18	**1b** (1.3)	LiHMDS (1.5)	*n*-C_4H_9OMs (1.0)	THF/HMPA	−98	0
19	**1b** (1.3)	LiHMDS (1.5)	CH_3CH_2OTf (1.0)	THF/HMPA	−98	97
20	**1b** (1.0)	LiHMDS (2.0)	*i*PrI (4.0)	THF/HMPA	−98	0
21	**1a** (1.0)	LiHMDS (1.5)	$Ph(CH_2)_3OTf$ (1.0)	THF/HMPA	−98	53

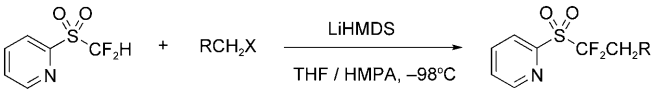
[a] THF/HMPA and Et_2O/HMPA were used in 10:1 (v/v) ratio. [b] Yield was determined by ^{19}F NMR spectroscopy with $PhCF_3$ as the internal standard. DMF = *N*,*N*-dimethylformamide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, Ms = mesyl, Py = pyridyl, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl, Ts = tosyl.

reaction temperature was further lowered to −78 °C with THF as the solvent. The addition of hexamethylphosphoramide (HMPA) was found to be necessary, which improved the yield to 45% when lithium hexamethyldisilazide (LiHMDS) was used as the base (Table 1, entries 5 and 6). Further lowering the temperature to −98 °C gave a considerably higher yield (Table 1, entry 7). Diethyl ether was also examined as the solvent, in which, a decreased yield was observed (Table 1, entry 8). Under similar conditions, other sulfones (**1a**, **1c**, and **1d**) were not significantly reactive (Table 1, entries 13–15). With exhaustive optimization of the proportion of the substrates, the best reaction conditions were established as 1.0 equivalent of iodide reacting with 1.3 equivalents of sulfone **1b** and 1.5 equivalents of LiHMDS in THF/HMPA (10:1, v/v) at −98 °C for 5 minutes (Table 1, entry 10). The additional investigation on the influence of metal cations (Na^+ and K^+; Table 1, entries 11 and 12) revealed that LiHMDS was the most suitable base. Other than alkyl iodides, alkyl bromides and triflates were also found to be reactive, and the latter exhibited the highest reactivity (Table 1, entries 16–19). A secondary alkyl iodide, however, did not give the anticipated product, thus indicating that the reaction is very sensitive to steric hindrance (Table 1, entry 20). Noticeably, although other difluoromethyl heteroaryl sulfones such as **1a** could also react with triflate, the yield was only moderate (Table 1, entry 21). Taking availability, stability, as well as high reactivity into account, the combination of alkyl halides and **1b** explicitly turns out to be advantageous in terms of the general applicability of the protocol.

Having established the reaction conditions, we further examined the scope of the current protocol (Table 2). The nucleophilic substitution was found to be very efficient with primary alkyl iodides, which afforded α,α-difluoroalkyl 2-pyridyl sulfones **3a**–**3i** in good yields (Table 2, entries 1–9). Notably, despite benzyl and allyl halides displaying fairly high reactivity (Table 2, entries 10-14), the corresponding products **3j**–**3n** were much more sensitive to the base than **3a**–**3i**, and readily underwent β elimination in the presence of excess base. In the case of 4-bromobenzyl bromide (Table 2, entry 11), the by-product 1,1-difluoroalkene could further react with the anion of **1b**, thus complicating the reaction.

Considering the ready availability of alcohols compared with alkyl halides, as an alternative route, the one-pot synthesis of substituted difluoromethyl sulfones **3** from alcohols was investigated (Table 3). By adopting triflates as intermediates, the primary alcohols **4** could be transformed into sulfones **3** in good yields (Table 3, entries 1–4). Owing to the lability of THF towards triflic anhydride,[13] Et_2O was chosen as the solvent in the first step. Intriguingly, 2-pyridyl sulfone **1b** itself could serve both as a base and as a pronucleophile during the course of the transformation. In the triflation step, **1b** was protonated to give a pyridinium salt and in the subsequent nucleophilic reaction step, it was recovered by an excess amount of base. Although triflates are essentially more reactive than alkyl halides, isopropyl triflate remained inert under the current chemical scenario (Table 3, entry 5).

Table 2: Preparation of substituted aifluoromethyl sulfones from halides.[a]

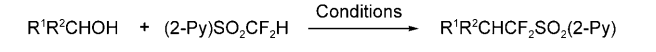


1b **2** **3**

Entry	Halide	Product	Yield [%][b]
1	CH_3CH_2I	**3a**, $CH_3CH_2CF_2SO_2$(2-Py)	74
2	$CH_3CH_2CH_2I$	**3b**, $CH_3CH_2CH_2CF_2SO_2$(2-Py)	73
3	$CH_3(CH_2)_2CH_2I$	**3c**, $CH_3(CH_2)_2CH_2CF_2SO_2$(2-Py)	78
4	$CH_3(CH_2)_3CH_2I$	**3d**, $CH_3(CH_2)_3CH_2CF_2SO_2$(2-Py)	75
5	$CH_3(CH_2)_5CH_2I$	**3e**, $CH_3(CH_2)_5CH_2CF_2SO_2$(2-Py)	69
6	$Ph(CH_2)_2CH_2I$	**3f**, $Ph(CH_2)_2CH_2CF_2SO_2$(2-Py)	88
7	$Ph(CH_2)_3CH_2I$	**3g**, $Ph(CH_2)_3CH_2CF_2SO_2$(2-Py)	73
8	$PhO(CH_2)_2CH_2I$	**3h**, $PhO(CH_2)_2CH_2CF_2SO_2$(2-Py)	71
9	$PhO(CH_2)_3CH_2I$	**3i**, $PhO(CH_2)_3CH_2CF_2SO_2$(2-Py)	73
10	$PhCH_2Br$	**3j**, $PhCH_2CF_2SO_2$(2-Py)	88
11	4-$BrC_6H_4CH_2Br$	**3k**, 4-$BrC_6H_4CH_2CF_2SO_2$(2-Py)	35[c] (82)
12	2,5-$Me_2C_6H_3CH_2I$	**3l**, 2,5-$Me_2C_6H_3CH_2CF_2SO_2$(2-Py)	99
13	4-vinyl-$C_6H_4CH_2I$	**3m**, 4-vinyl-$C_6H_4CH_2CF_2SO_2$(2-Py)	78
14	$CH_2{=}CHCH_2I$	**3n**, $CH_2{=}CHCH_2CF_2SO_2$(2-Py)	76

[a] All reactions were performed under the optimized conditions. [b] Yield of isolated product after flash column chromatography. The yield in parentheses was determined by ^{19}F NMR spectroscopy. [c] Yield after recrystallization, which was carried out twice. HMPA = hexamethyl phosphoramide.

Table 3: One-pot synthesis of substituted difluoromethyl sulfones from alcohols.



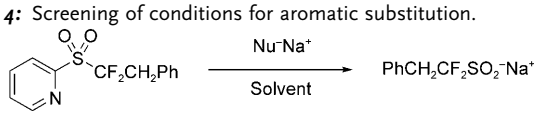
4 **1b** **3**

Entry[a]	R^1	R^2	Product	Yield [%][b]
1	CH_3	H	**3a**	82
2	$CH_3(CH_2)_5$	H	**3e**	62
3	$Ph(CH_2)_2$	H	**3f**	87
4	$Ph(CH_2)_3$	H	**3g**	79
5	CH_3	CH_3	**3o**	0

[a] Reaction conditions: 1. Tf_2O, Et_2O, 0 °C, 30 min; 2. LiHMDS, THF/HMPA (10:1), −98 °C, 5 min. [b] Yield of isolated product.

With a series of substituted difluoromethyl 2-pyridyl sulfones **3** on hand, we continued our investigation on the preparation of difluoroalkylsulfonates. Considering the baselability of the benzyl-substituted compounds, the sulfone **3j** was selected as a model substrate for the establishment of appropriate dearylation conditions (Table 4). Among a series of nucleophiles that were examined (Table 4, entries 1–7), the less basic sodium ethanethiolate (EtSNa) was identified as the most promising reagent owing to the highest yield of sulfinate **5** in comparison with others (Table 4, entry 2). Subsequently, using EtSNa as the optimal nucleophile (Table 4, entries 8–16), a screening of solvents showed that the highest yield of sulfinate **5** could be obtained in THF (Table 4, entry 10). In particular, although only low conversion was achieved in ethanethiol, the selectivity of the reaction (yield/conversion) was found to be remarkably higher under buffered conditions

Table 4: Screening of conditions for aromatic substitution.



3j **5**

Entry	Nucleophile (equiv)	Solvent	t [h]	Conv. [%][a]	Yield [%][a]
1	EtONa (1.6)	CH_3CN	3	quant.	0
2	EtSNa (2.0)	CH_3CN	3	88	50
3	PhSNa (2.0)	CH_3CN	24	10	0
4	tBuSNa (2.0)	CH_3CN	20	33	0
5	$NaBH_4$ (2.0)	MeOH	24	7	0
6	NaCN (4.0)	DMF	20	0	0
7	$NaCH(CN)_2$ (4.0)	DMF	20	0	0
8	EtSNa (2.0)	EtOH	24	quant.	0
9	EtSNa (2.0)	CH_2Cl_2	12	0	0
10	**EtSNa (2.0)**	**THF**	**12**	**86**	**71**
11	EtSNa (2.0)	$PhCH_3$	12	5	0
12	EtSNa (2.0)	DMF	12	quant.	60
13	EtSNa (2.0)	acetone	12	79	45
14	EtSNa (2.0)	Et_2O	12	30	15
15	EtSNa (2.0)	tBuOH	2	63	15
16	**EtSNa (2.0)**	**EtSH**	**20**	**10**	**10**
17	**EtSNa (2.0)**	**EtSH/THF (1:2)**	**12**	**quant.**	**quant.**
18[b]	EtSNa (2.0)	EtSH/THF (1:2)	12	0	0

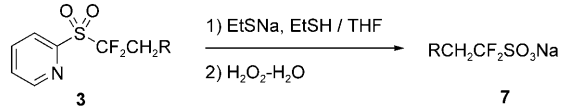
[a] Determined by ^{19}F NMR spectroscopy. [b] $PhSO_2CF_2CH_2CH_3$ (**6**) was used.

(Table 4, entry 16). Encouragingly, using ethanethiol/THF (1:2, v/v) as a buffered solvent system, the reaction proceeded smoothly to provide the sulfinate **5** in quantitive yield with excellent selectivity (Table 4, entry 17). However, phenyl sulfone **6** failed to be converted under these reaction conditions (Table 4, entry 18), thus indicating the necessity of the 2-pyridyl group in this transformation.

The optimized reaction conditions developed for the transformation of sulfone **3j** were applied to other difluorinated sulfones. With the combined dearylation–oxidation procedure, the α,α-difluoroalkyl sulfonates **7** could be prepared from **3** in one pot in excellent yield and high purity (Table 5). In addition to the simple sulfonates, the current protocol was applied for the conversion of a variety of substrates bearing bromine, phenoxy, and vinyl groups—such products are rarely available. Notably, the vinyl group is amenable to the oxidation with hydrogen peroxide to afford the vinyl-containing sulfonates **7m** and **7n** that are highly useful for further polymerization (Table 5, entries 13 and 14).

To further demonstrate the synthetic utility of this protocol, an efficient synthesis of an α,α-difluorosulfonate analogue of sulfated carbohydrate was performed (Scheme 3). Compound **11** (with Li^+ as the cation), which has been previously prepared by electrophilic fluorination of a protected sulfonate precursor, was obtained in only moderate yield owing to its rapid decomposition to 1,1-difluoro-1-alkene under the basic reaction conditions.[6d] By the means of novel nucleophilic difluoro(sulfonato)methylation reaction, starting from the triflate **8**, the benzyl-protected β-pyranoside sulfonate **10** was obtained in 85 % overall yield, and can further afford fluorinated carbohydrate sulfonate **11** through the removal of the benzyl groups.

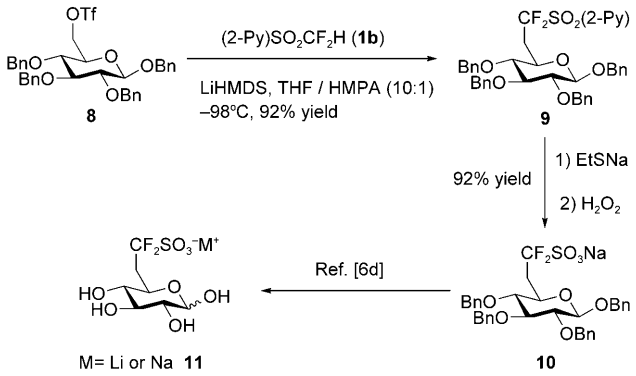
Table 5: Synthesis of various difluorinated sulfonates.



3 **7**

Entry	Sulfone	Sulfonate	Yield (purity) [%][a]
1	$CH_3CH_2CF_2SO_2$(2-Py)	**7a**, $CH_3CH_2CF_2SO_3Na$	99 (95)
2	CH_3 $CH_2CH_2CF_2SO_2$(2-Py)	**7b**, $CH_3CH_2CH_2CF_2SO_3Na$	96 (98)
3	$CH_3(CH_2)_2CH_2CF_2SO_2$(2-Py)	**7c**, $CH_3(CH_2)_2CH_2CF_2SO_3Na$	94 (98)
4	$CH_3(CH_2)_3CH_2CF_2SO_2$(2-Py)	**7d**, $CH_3(CH_2)_3CH_2CF_2SO_3Na$	99 (95)
5	$CH_3(CH_2)_5CH_2CF_2SO_2$(2-Py)	**7e**, $CH_3(CH_2)_5CH_2CF_2SO_3Na$	99 (97)
6	$Ph(CH_2)_2CH_2CF_2SO_2$(2-Py)	**7f**, $Ph(CH_2)_2CH_2CF_2SO_3Na$	96 (98)
7	$Ph(CH_2)_3CH_2CF_2SO_2$(2-Py)	**7g**, $Ph(CH_2)_3CH_2CF_2SO_3Na$	98 (95)
8	$PhO(CH_2)_2CH_2CF_2SO_2$(2-Py)	**7h**, $PhO(CH_2)_2CH_2CF_2SO_3Na$	97 (95)
9	$PhO(CH_2)_3CH_2CF_2SO_2$(2-Py)	**7i**, $PhO(CH_2)_3CH_2CF_2SO_3Na$	97 (95)
10	$PhCH_2CF_2SO_2$(2-Py)	**7j**, $PhCH_2CF_2SO_3Na$	90 (99)
11	4-$BrC_6H_4CH_2CF_2SO_2$(2-Py)	**7k**, 4-$BrC_6H_4CH_2CF_2SO_3Na$	92 (95)
12	2,5-$Me_2C_6H_3CH_2CF_2SO_2$(2-Py)	**7l**, 2,5-$Me_2C_6H_3CH_2CF_2SO_3Na$	96 (97)
13	4-vinyl-$C_6H_4CH_2CF_2SO_2$(2-Py)	**7m**, 4-vinyl-$C_6H_4CH_2CF_2SO_3Na$	96 (95)
14	CH_2=$CHCH_2CF_2SO_2$(2-Py)	**7n**, CH_2=$CHCH_2CF_2SO_3Na$	90 (99)

[a] Yield of isolated product. Purity was determined by ^{1}H NMR spectroscopy.

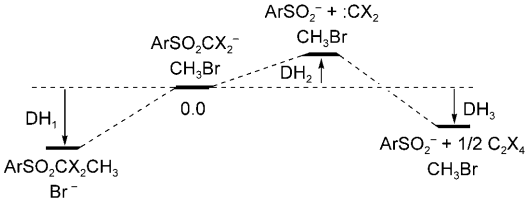


Scheme 3. Synthesis of fluorinated β-pyranoside sulfonate **11**. Bn = benzyl.

Finally, to manifest the structure–reactivity relationship observed for various aryl sulfones, computational studies based on the density functional theory (DFT) were performed at the B3LYP/6-311 + G(2d,p) level.[14] As shown in Table 6, significantly lower bond orders were found to be associated with difluoromethides (**12b**–**12f**), thus indicating weaker S–CX_2 bonds compared with the non-fluorinated analogue (**12a**). In contrast with the S–CH_2 bond in **12a** that possesses partial double bond character, the S–CF_2 bond lengths are calculated to be much longer than that of the typical C_{sp^3}–SO_2 bonds (1.764–1.790 Å),[15] thus suggesting the absence of resonance. These results explicitly rationalize the superior stability of **12a** over **12b**–**12f**, which readily degrade into difluorocarbene and the corresponding sulfinates under the reaction conditions (see above). Moreover, according to the computational studies, the Mulliken charges on the anionic carbon atoms was found to increase from **12b** to **12f**, thus revealing a gradual decrease in nucleophilicity of the fluorinated carbanions.

Apart from the electronic profiles of the intermediates, the thermodynamic aspects of the reactions were further investigated. As depicted in Table 6, all the nucleophilic substitution reactions are shown to be thermodynamically favorable at the B3LYP/6-311 + G level.[14] Moreover, the reactions of CH_3Br with **12b** and **12c** are of substantial energetic preference over those involving **12d**–**12f**, and is in good agreement with the experimental outcomes. The cleavage of the S–CX_2 bond was also found to be thermodynamically allowed in light of the dimerization of the carbenes; however, in comparison with **12d**–**12f**, the decomposition of **12b**,**c** is less likely to occur due to the formation of thermodynamically less stable sulfinates. Notably, even though the decomposition of **12a** into the corresponding sulfinate and ethylene is energetically rather favorable than that of **12b** and **12c**, the carbene intermediate (:CH_2) exhibits much less stability than the difluorocarbene (:CF_2). Therefore, the facile nucleophilic substitution of **12b** and **12c** towards alkyl halides can be rationalized as consequences of both energetically favored formation of the products and relatively difficult decomposition regimen. Particularly, the lower reactivity of **12c** in

Table 6: Structural parameters associated with arylsulfonylmethide anions.



Ar–S(=O)(=O)–CX_2^-	Bond order[a] S–CX_2	Bond length [Å] S–CX_2	Mulliken charge ($Q_{anionic\ C}$)	ΔG [kcal mol^{-1}] ΔG_1	ΔG_2	ΔG_3
$PhSO_2CH_2^-$ (**12a**)	1.028	1.664	−0.432	−51.0	+75.3	−25.2
$PhSO_2CF_2^-$ (**12b**)	0.733	1.873	+0.010	−51.3	+18.0	−18.9
2-$PySO_2CF_2^-$ (**12c**)	0.753	1.868	+0.053	−51.4	+16.2	−20.7
4-$NPSO_2CF_2^-$ (**12d**)	0.761	1.846	+0.085	−39.5	+14.7	−22.2
$BTSO_2CF_2^-$ (**12e**)	0.786	1.851	+0.092	−43.9	+11.1	−25.8
$PTSO_2CF_2^-$ (**12f**)	0.753	1.859	+0.145	−37.7	+5.2	−31.7

[a] Atom–atom overlap-weighted NAO (natural atomic orbital) bond order.

DMF, compared with **12b**, can be attributed to its low nucleophilicity and high lability.

In conclusion, we have reported an efficient method for the synthesis of alkyl α,α-difluorosulfonates from difluoromethyl 2-pyridyl sulfone, which represents the first nucleophilic difluoro(sulfonato)methylation reaction. The selection of a suitable aryl substitute is critically important for the successes of this transformation, which facilitates both the nucleophilic fluoroalkyl substitution reaction as well as the subsequent dearylation. This research not only extends the synthetic application of fluorinated sulfones, but also provides a unique solution for the long-standing challenge in the nucleophilic difluoro(sulfonato)methylation reaction. Further research on the synthetic use of fluoroalkyl heteroaryl sulfone derivatives is currently underway.

Experimental Section

Typical procedure for the reaction between difluoromethyl sulfone and halides: Under an atmosphere of N_2, into a 100 mL Schlenk flask containing 1-iodoheptane (678 mg, 3.0 mmol) and 2-$PySO_2CF_2H$ (**1b**; 754 mg, 3.9 mmol) in THF (30 mL), was added HMPA (3 mL), then the reaction mixture was cooled to −98 °C using a CH_3OH/liquid N_2 cold bath. A solution of $(TMS)_2NLi$ (LiHMDS, 756 mg, 4.5 mmol) in THF (5 mL) was added over 5 min and the reaction mixture was immediately quenched with saturated NH_4Cl aqueous solution (3 mL) at the same temperature. After removal of the cold bath, water (30 mL) was added. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic phase was dried over $MgSO_4$. After the removal of solvents under reduced pressure, the crude residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, from 3:1 to 2:1) to give **3e** (612 mg, 69% yield).

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