

Nucleophilic difluoromethylation of carbonyl compounds using $\text{TMSCF}_2\text{SO}_2\text{Ph}$ and Mg^0 -mediated desulfonylation

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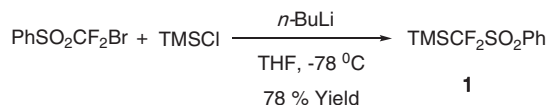
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Abstract—A new nucleophilic difluoromethylation chemistry using fluoride-induced (phenylsulfonyl)difluoromethylation with $\text{TMSCF}_2\text{SO}_2\text{Ph}$ followed by the magnesium-metal-mediated desulfonylation has been achieved. This methodology is compatible with both enolizable and non-enolizable aldehydes and ketones and has special advantage in the case of enolizable aldehydes. The new efficient desulfonylation method is considered to be environmentally benign due to the absence of mercury.
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Selective incorporation of fluorine-containing building blocks into organic compounds, commonly called ‘fluoroalkylation’, is a widely employed and powerful strategy in drug design and materials research.¹ Nucleophilic fluoroalkylation (such as trifluoromethylation) of carbonyl compounds has been proven to be a convenient method for the preparation of fluorinated compounds.² However, although nucleophilic trifluoromethylation of carbonyl compounds has been extensively studied and eventually tamed with TMSCF_3 reagent elegantly developed by Prakash and Olah,³ its analogous difluoromethylation of carbonyl compounds is more challenging regarding the generality and efficiency.⁴ Difluoromethyl group (CF_2H) is known to be isosteric to a carbinol group (CH_2OH), and it can behave as a lipophilic hydrogen donor through hydrogen bonding.⁵ Several methods have been attempted to tackle the nucleophilic difluoromethylation of carbonyl compounds. Both (difluoromethyl)trialkylsilanes ($\text{R}_3\text{SiCF}_2\text{H}$)⁴ and bis(trimethylsilyl)difluoromethane⁶ were found not to be general difluoromethylating agents, and recently one of us was involved in the development of nucleophilic difluoromethylation of carbonyl compounds using difluoromethyl phenyl sulfone ($\text{PhSO}_2\text{CF}_2\text{H}$).⁷ Although the difluoromethylation method with $\text{PhSO}_2\text{CF}_2\text{H}$ is amenable to many non-enolizable and enolizable aldehydes and ke-

tones, it has the following three drawbacks: (1) the method requires the use of excess amount of base (LHMDS) and carbonyl compounds in order to obtain good yields of the products; (2) the method is rather ineffective with enolizable aldehydes; (3) the desulfonylation step requires the toxic sodium/mercury amalgam.⁷ As our continuing effort in developing efficient fluoroalkylation methodologies, herein we wish to reveal our improved nucleophilic difluoromethylation of carbonyl compounds using [(phenylsulfonyl)difluoromethyl]trimethylsilane ($\text{TMSCF}_2\text{SO}_2\text{Ph}$, **1**) and magnesium-metal-mediated reductive desulfonylation.

$\text{TMSCF}_2\text{SO}_2\text{Ph}$ was first prepared by oxidation of TMSCF_2SPh using *m*-chloroperbenzoic acid (*m*-CPBA),⁸ but we found the desilylative hydrolysis happened readily during the basic workup (in order to neutralize the *m*-chlorobenzoic acid by-product), which decreased the yields of **1**. Finally, we were able to prepare compound **1** in good yield by the reaction of bromodifluoromethyl phenyl sulfone,⁸ TMSCl , and *n*-BuLi in THF at -78°C (see Scheme 1).⁹ We found that compound **1** can also be prepared from the reaction of difluoromethyl phenyl sulfone, TMSCl , and *n*-BuLi under the similar reaction conditions.



Scheme 1. Preparation of $\text{TMSCF}_2\text{SO}_2\text{Ph}$.

Keywords: Difluoromethylation; Fluorine; Magnesium; Desulfonylation.

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Table 1. Nucleophilic (phenylsulfonyl)difluoromethylation of carbonyl compounds **2** with **1**

$ \begin{array}{ccc} \text{R}^1-\text{C}(=\text{O})-\text{R}^2 & \xrightarrow[\text{(2) } n\text{-Bu}_4\text{NF, THF-H}_2\text{O or H}_3\text{O}^+]{\text{(1) TMSCF}_2\text{SO}_2\text{Ph (1), "F"}^-(5 \text{ mol}\%), \text{ THF, } -78^\circ\text{C to r.t.}} & \text{HO}-\text{C}(\text{CF}_2\text{SO}_2\text{Ph})(\text{R}^1)(\text{R}^2) \\ \mathbf{2} & & \mathbf{3} \end{array} $				
Entry	Carbonyl compound 2	Initiator	Product 3	Yield (%) ^a
1		TBAT		81
2		TBAT		86
3		TBAT		92
4		TBAT		84 ^c
5		TBAT		73
6	$(\text{CH}_3)_2\text{CHO}$	TBAT		83
7		TBAT		81
8		TBAT		70
9		CsF ^b		93
10		CsF		79
11		CsF		50
12		CsF		53 ^c

^a Isolated yield.^b When TBAT was used, no desired reaction occurred and reagent **1** was transformed into PhSO₂CF₂H.^c Only 1,2-addition product was obtained.

With compound **1** in hand, we examined its applications in the fluoride-induced (phenylsulfonyl)difluoromethylation of aldehydes and ketones. It was found that a variety of structurally diverse aldehydes and ketones can be readily (phenylsulfonyl)difluoromethylated in good yields by using this new method.¹⁰ The results are summarized in Table 1. It is particularly remarkable that enolizable aldehydes can also give the corresponding products **3** in 73–83% yields (entries 5–7), which is superior to the previously reported difluoromethylations with $\text{PhSO}_2\text{CF}_2\text{H}$.⁷ In the case of α,β -unsaturated aldehyde and ketone, only 1,2-addition products were obtained (entries 4 and 12). It is interesting that the reactions with ketones were dramatically affected by the fluoride sources (entries 9–12), which was not observed during the reaction of TMSCF_2SPh .¹¹ When tetrabutylammonium triphenyldifluorosilicate (TBAT) was applied as the fluoride initiator for the reaction of acetophenone with **1**, no desired reaction took place. When cesium fluoride (CsF) was used, the same reaction was able to give the addition product **3i** in 93% yield! With the use of CsF, other ketones can react with **1** to give the corresponding products in moderate to good yields (entries 10–12). This difference appears to be due to the steric bulk of both tetrabutylammonium counterion and phenylsulfonyl group.^{2a,12} Compared with acyclic ketones, cyclic ketones showed higher reactivity toward **1** and TBAT is still efficient enough to initiate the reaction (entry 8).

Having achieved the success of fluoride-induced (phenylsulfonyl)difluoromethylation with **1**, we turned our next goal to develop an inexpensive and environmentally benign desulfonylation method. Desulfonylation reactions are usually performed using the reducing agents such as Na/Hg amalgam,^{13,14} SmI_2/HMPA ,¹⁵ Mg/HgCl_2 ,¹⁶ which are usually toxic due to the mercury and HMPA species. On the basis of our previous work with magnesium-metal-mediated reactions,⁹ we envisioned that the inexpensive and readily available magnesium metal (without mercury additive) might be suitable

for the reductive desulfonylation of carbinols **3**. Compound **3i** was set as a model compound to optimize the desulfonylation reaction conditions (see Table 2). However, the reaction was very sluggish when H_2O was used as proton donor (entry 1). We tried to add HOAc into the system, which was expected to serve as both an activator for magnesium metal and a proton source. To our great joy, the desulfonylation reaction occurred readily with high conversion (entry 2).

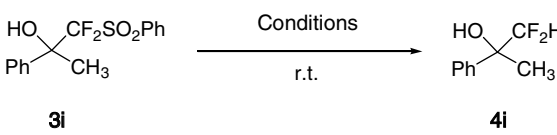
Inspired by this result, we examined other solvents and proton sources and finally found the polar solvent DMF or DMSO was the solvent of choice and HOAc/NaOAc buffer solution was the best proton donor (entries 3 and 5). Zinc, aluminum, and triphenylphosphine were found not to be effective desulfonylating agents, and THF was not a good solvent for the reaction (entries 7–10).

By employing $\text{Mg}/\text{HOAc}/\text{NaOAc}$ desulfonylation system in $\text{DMF}/\text{H}_2\text{O}$ (5:1) mixed solvents, a variety of (phenylsulfonyl)difluoromethylated carbinols **3** can be effectively transformed into difluoromethyl alcohols **4** in good to excellent yields (see Table 3).¹⁷ This new type of desulfonylation reactions can be commonly completed in 1–2 h at ambient temperature and it is compatible with several functional groups as shown in Table 3. This magnesium-metal-mediated reductive desulfonylation method promises to be an environmentally benign alternative for the conventional approach using Na/Hg amalgam.

Concerning the mechanism of this novel type of nucleophilic difluoromethylation of carbonyl compounds **2** with reagent **1**, it is similar to the one as proposed earlier by Prakash and co-workers in the case of trifluoromethylation with TMSCF_3 ,³ which is shown in Scheme 2.

In summary, an improved nucleophilic difluoromethylation of carbonyl compounds has been achieved by using $\text{TMSCF}_2\text{SO}_2\text{Ph}$ (**1**) as the difluoromethylating

Table 2. Reaction condition optimization of mercury-free reductive desulfonylation

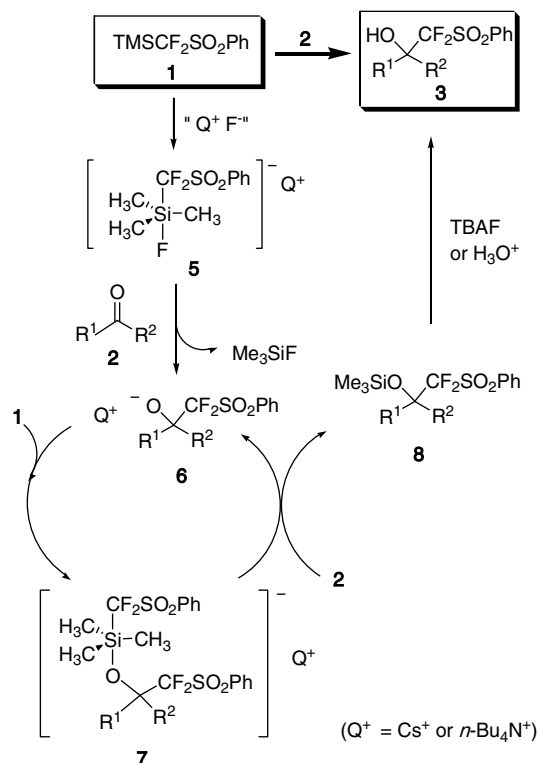
					
Entry	Reducing agent (equiv)	Solvent	Proton source	Reaction time (h)	Conversion (%) ^a
1	Mg (25)	DMF	H_2O	24	<5
2	Mg (25)	DMF	HOAc/ H_2O	1	90
3	Mg (15)	DMF	HOAc/NaOAc	3	96
4	Mg (15)	DMF	NH_4Cl (sat.)	12 ^b	90
5	Mg (10)	DMSO	HOAc/ H_2O	3	92
6	Mg (15)	MeOH	HCl (6 N)	3	<10
7	Mg (15)	THF	HOAc/ H_2O	3	0
8	Zn (15)	DMF	HOAc/NaOAc	12	0
9	Al (10)	DMF	HOAc/NaOAc	12	0
10	PPh_3 (15)	DMF	HOAc/NaOAc	12	0

^a Conversions were determined by ^{19}F NMR spectroscopy.

^b Prolonged reaction time was required due to the low solubility of NH_4Cl in DMF.

Table 3. Reductive desulfonylation using $\text{Mg}^0/\text{HOAc}/\text{AcONa}$ system in DMF/ H_2O (5:1) at room temperature

Entry	Carbinol 3	Product 4	Yield (%) ^a
1			91
2			83
3			86
4			88
5			89
6			84
7			87
8			83
9			80

^a Isolated yields.**Scheme 2.** Proposed mechanism of nucleophilic difluoromethylation of **2** with **1**.

agent for the first time. A new environmentally benign reductive desulfonylation method has been developed using $\text{Mg}^0/\text{HOAc}/\text{NaOAc}$ system. The overall difluoromethylation procedure has many advantages over the other known ones, and it promises to be a highly useful synthetic tool for many other potential applications. Moreover, the counterion effect was observed and the use of this interaction for enantioselective difluoromethylation of aldehyde with a chiral tetraalkylammonium fluoride as the chiral inducer is underway in our laboratory.

Acknowledgments

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9. Preparation of [(phenylsulfonyl)difluoromethyl]trimethylsilane (**1**): *n*-Butyllithium in hexane (1.6 M, 20.7 mL, 33.2 mmol) was added into the solution of bromodifluoromethyl phenyl sulfone (5.0 g, 18.4 mmol) and chlorotrimethylsilane (3.8 mL, 27.7 mmol) in THF (50 mL) at -78°C , and the mixture was stirred for 1 h at the same temperature. Then the reaction was quenched with cold saturated aqueous NH_4Cl solution, and the reaction mixture was extracted with Et_2O (50 mL $\times$ 3). The combined organic phase was washed with brine, and water, and then dried over anhydrous NaSO_4 . After solvent removal, the crude product was fractionally distilled to afford 3.8 g (78% yield) of product **1** as a colorless liquid, bp $102\text{--}104^{\circ}\text{C}/1\text{ Torr}$. ^1H NMR (CDCl_3): δ 0.42 (s, 9H); 7.60 (t, $J = 7.5\text{ Hz}$, 2H); 7.73 (t, $J = 7.5\text{ Hz}$, 1H); 7.94 (d, $J = 8.0\text{ Hz}$, 2H). ^{19}F NMR (CDCl_3): δ -112.9 (s). The data are consistent with the previous report.⁸
10. Typical procedures for fluoride-induced (benzenesulfonyl)-difluoromethylation of carbonyl compounds: Under N_2 atmosphere, into a 25-mL Schlenk flask containing 2-naphthaldehyde (**2a**, 78 mg, 0.5 mmol) and $\text{TMS-CF}_2\text{SO}_2\text{Ph}$ (**1**, 0.6 mmol) in dry THF (2.5 mL) at -78°C , was added dropwise a THF solution (1.5 mL) of tetrabutylammonium triphenyldifluorosilicate (TBAT, 13 mg, 0.05 mmol). The reaction mixture was slowly warmed to room temperature with stirring overnight. Then a THF solution of TBAF (1.0 mol/L, 0.65 mL) was then added and the whole mixture was stirred for another 30 min followed by adding 5 mL of brine. The solution mixture was extracted with Et_2O (15 mL $\times$ 3), and the combined organic phase was dried over MgSO_4 . After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography using petroleum ether/ethyl acetate (6:1) as eluent to give product **3a** as a white solid, yield 81% (141 mg). Mp $98\text{--}100^{\circ}\text{C}$. ^1H NMR (CDCl_3): δ 3.67 (s, 1H); 5.77 (d, $J = 12\text{ Hz}$, 1H); 7.35–8.15 (m, 12H). ^{13}C NMR (CDCl_3): δ 71.39 (dd, $J = 26, 19.6\text{ Hz}$); 120.41 (dd, $J = 297, 287\text{ Hz}$); 124.92; 126.35; 126.70; 127.64; 128.0; 128.18; 128.22; 129.24; 130.57; 131.14; 132.82; 132.84; 133.71; 135.43. ^{19}F NMR (CDCl_3): δ -103.8 (d, $J = 237\text{ Hz}$, 1F); -121.5 (dd, $J = 237, 21\text{ Hz}$, 1F). MS (EI, m/z): 348 (M^+). EA: calcd for $\text{C}_{18}\text{H}_{14}\text{F}_2\text{O}_3\text{S}$: C, 62.06; H, 4.05. Found: C, 61.85; H, 4.10.
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17. Typical procedure for magnesium-mediated desulfonylation: Into a 50-mL Schlenk flask containing sulfone compound **3a** (250 mg, 0.7 mmol) in 7.5 mL DMF at room temperature was added 4 mL of HOAc/NaOAc (1:1) buffer solution (8 mol/L). Magnesium turnings (252 mg, 10.5 mmol) were added in portions. The reaction mixture was stirred at room temperature for 3 h followed by adding 30 mL of water. The solution mixture was extracted with Et_2O (20 mL $\times$ 3), and the combined organic phase was washed with saturated NaHCO_3 solution and brine, then dried over MgSO_4 . After the removal of ethyl ether, the crude product was purified by silica gel column chromatography using petroleum ether/ethyl acetate (8:1) as eluent to give product **4a** as a white solid 133 mg (91% yield). Mp $59\text{--}61^{\circ}\text{C}$. ^1H NMR (CDCl_3): δ 2.93 (s, 1H); 5.86 (td, $J = 56.2, 4.7\text{ Hz}$, 1H); 4.95 (td, $J = 10.1, 4.7\text{ Hz}$, 1H); 7.45–7.60 (m, 3H); 7.80–7.92 (m, 4H). ^{13}C NMR (CDCl_3): δ 73.74 (t, $J = 24.5\text{ Hz}$); 115.84 (t, $J = 245\text{ Hz}$); 124.30; 126.44; 126.55; 126.61; 127.72; 128.11; 128.47; 133.06; 133.24; 133.52. ^{19}F NMR (CDCl_3): δ -127.3 (ddd, $J = 284, 56, 9\text{ Hz}$, 1F); -127.9 (ddd, $J = 284, 56, 10\text{ Hz}$, 1F). MS (EI, m/z): 208 (M^+). HRMS (EI): m/z calcd for $\text{C}_{12}\text{H}_{10}\text{F}_2\text{O}$ (M^+) 208.0697, found 208.0699. The data are consistent with the previous report.¹¹