Convenient Synthesis of Difluoromethyl Alcohols from Both Enolizable and Non-Enolizable Carbonyl Compounds with Difluoromethyl Phenyl Sulfone

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A general and efficient nucleophilic difluoromethylation of carbonyl compounds (both enolizable and non-enolizable aldehydes and ketones) has been achieved by using a nucleophilic (phenylsulfonyl)difluoromethylation-reductive desulfonylation strategy. Difluoromethyl phenyl sulfone acts as a difluoromethyl anion ("CF_2H^-") equivalent.

Introduction

Selective incorporation of difluoromethyl group (CF_2H) into organic molecules has attracted much interest since it plays critical roles in the bioactive molecules as a lipophilic isostere of hydroxy group (OH) as well as a hydrogen donor through hydrogen bonding.[1] Although several methods are available to introduce a difluoromethyl group into organic substrates without an α-hydroxy group, few methods have been reported for the preparation of α-difluoromethyl alcohols.[2] Nucleophilic trifluoromethylation of carbonyl compounds are well-developed and widely used, especially with (trifluoromethyl)trimethylsilane (TMS–CF_3), first developed by us in 1989.[3] However, its analogous nucleophilic difluoromethylation is more challenging regarding the generality and efficiency. This is mainly due to the fact that Si–CF_2H (bond order 0.436) is less polarized than the Si–CF_3 bond (bond order 0.220), indicating that the cleavage of former bond is much more difficult.[4] Fuchikami and co-workers have attempted the fluoride-induced difluoromethylation of carbonyl compounds with difluoromethylsilane derivatives in DMF, and found that the reaction requires high temperature (100 °C) and give poor yields with ketones.[4] Stahly reported the difluoromethylation of aldehydes with difuoromethyl phenyl sulfone, but the method is only limited to non-enolizable aldehydes.[5] In 1997, we reported the fluoride-induced difluoromethylation of carbonyl compounds with $Me_3SiCF_2SiMe_3$ at room temperature.[6] Although the reaction worked well with both enolizable and non-enolizable aldehydes, it could not be applied to ketones.[6] Therefore, there is still lack of a general and efficient difluoromethylation method applicable to both enolizable and non-enolizable aldehydes and ketones. As our continuing effort, herein we wish to disclose an efficient nucleophilic difluoromethylation of both enolizable and non-enolizable aldehydes and ketones, using difuoromethyl phenyl sulfone as a difluoromethyl anion ("CF_2H^-") equivalent.

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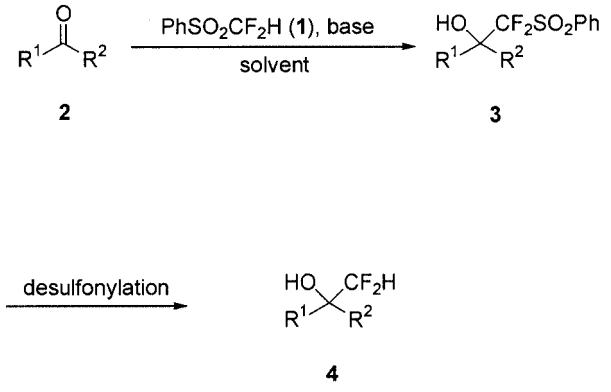
Results and Discussion

Previously, we have reported that difluoromethyl phenyl sulfone (**1**)[7] can act as a selective difluoromethylene dianion equivalent ("$^-CF_2^-$") in the one-pot stereoselective synthesis of *anti*-2,2-difluoropropane-1,3-diols,[8] a difluoromethylidene equivalent ("$=CF_2$") in the synthesis of 1,1-difluoro-1-alkenes,[9] and a difluoromethyl anion equivalent ("CF_2H^-") in the synthesis of difluoromethylsilanes[10] and difluoromethylalkanes.[11] The chemistry is mostly based on the selective deprotonation of the acidic CF_2H proton of **1** with a base (commonly *t*BuOK), to in situ generate a (phenylsulfonyl)difluoromethyl anion ($PhSO_2CF_2^-$), and the latter species further reacts with electrophiles.[8,9,11] We attempted to apply a similar protocol in the difluoromethylation of carbonyl compounds (see Scheme 1), i.e., to synthesize the (phenylsulfonyl)difluoromethylated carbinols **3**, followed by selective desulfonylation to give difluoromethyl carbinols **4**. However, when **1**/*t*BuOK reacted with benzaldehyde in DMF at –50 °C to room temp., 2,2-difluoro-1,3-diphenyl-1,3-propanediol was formed as a byproduct in significant amounts (30–40%), which decreased the product yield. Obviously, here *t*BuOK also acts as a nucleophile to further activate the C–S bond cleavage of the product **3**.[8,12] Furthermore, the reactions of **1**/*t*BuOK system with enolizable aldehydes and ketones at –50 °C to room temp. gave

very poor yields of product (10–30%). It soon became apparent that the use of a proper base is critical for this reaction. The base has to satisfy the following two requirements: First, it should be a reasonably strong base (for deprotonating **1** to generate $PhSO_2CF_2^-$) but a weak nucleophile (unlike *t*BuOK), in order to avoid the C–S bond cleavage during the reaction; second, the base has to be able to kinetically effect the deprotonation of **1** rather than the unwanted enolization of the carbonyl compounds at low temperature. We have scanned a variety of bases including triethylamine, pyridine, *n*-butyllithium, potassium hexamethyldisilazide and lithium hexamethyldisilazide (LHMDS), and finally found that LHMDS[13] is the base of choice. We have also noticed that McCarthy[14] and Boger[15] have also applied LHMDS as a base in their preparations of 1,1-difluoroalkenes from carbonyl compounds. Others have also applied LDA[20] and LHMDS[21] for the reactions between $PhSO_2CF_2H$ and ketones.



Scheme 1. Difluoromethylation of carbonyl compounds using **1**.

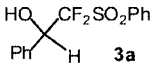
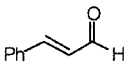
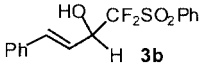
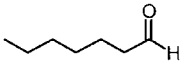
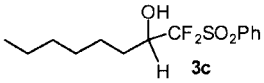
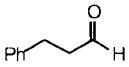
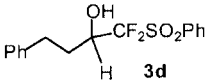
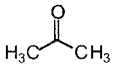
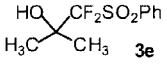
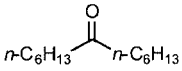
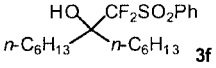
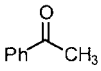
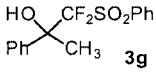
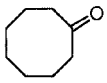
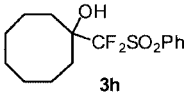
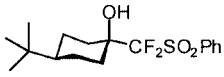
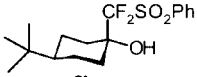
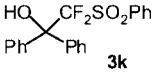
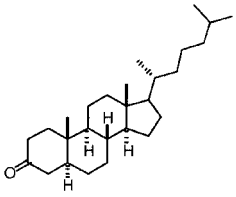
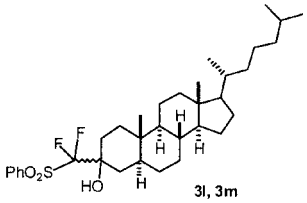
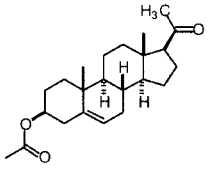
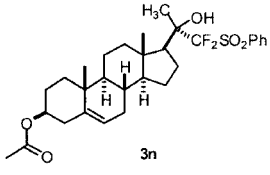
A typical reaction was carried out as follows: LHMDS (2 equiv., dissolved in THF) was slowly added into a mixture of **1** (1 equiv.) and carbonyl compounds (2 equiv.) in THF/HMPA (10:1) at –78 °C, and the reaction mixture was kept at this temperature and stirred for 1.5–8.0 h. The addition of hexamethylphosphoramide (HMPA)[16] as a cosolvent was found to be helpful in shortening the reaction time and enhancing the yields. A variety of structurally diverse carbonyl compounds (both enolizable and non-enolizable aldehydes and ketones) have been used for this reaction, and the results are summarized in Table 1. As shown in Table 1, the reaction works equally well with most aldehydes and ketones to give the (phenylsulfonyl)difluoromethyl carbinols **3** in high yields. It is remarkable that with the enolizable substrates, such as acetone (see Table 1, Entry 5), the expected product **3e** was formed in 92% yield. This indicates that at –78 °C, both reaction rates of deprotonation of **1** with LHMDS and nucleophilic addition of $PhSO_2CF_2^-$ into carbonyl group are much faster than that of the unwanted enolization reaction. When the same reaction was carried out at room temperature, much poorer yield of product was obtained, indicating that the kinetic resolution plays a key role for the success of the reaction at –78 °C. Enolizable aldehydes as expected showed more sensitivity to LHMDS than the enolizable ketones, and relatively lower yields of products were obtained (see Entries 3 and 4). In the cases of Entries 3 and 4, after the reactions, unreacted aldehydes were recovered and only small amounts of aldol side-reaction products were observed. For the α,β-unsaturated aldehyde, only 1,2-addition product **3b** was observed (Entry 2). In the case of 4-(*tert*-butyl)cyclohexanone, both equatorial and axial addition products **3i** and **3j** were isolated in 5:8 ratio (see Entry 9). The reaction with benzophenone only gave 61% yield of product **3k** (Entry 10), probably due to the steric hindrance between the $PhSO_2CF_2^-$ anion and two phenyl rings of benzophenone. More remarkably, the chemistry also works with complex molecules such as steroids (see Table 1, Entries 11 and 12). For 5α-cholestan-3-one, both axial and equatorial addition products **3l** and **3m** were obtained in 9:5 ratio (Table 1, Entry 11). A high diastereoselective addition reaction was observed with pregnenolone acetate, to give the product **3n** in 81% yield with > 99% *de* (Table 1, Entry 12).

Reductive desulfonylation is a widely used method in organic synthesis.[17] However, the reductive desulfonylation of *gem*-difluorinated sulfones are scarce. Stahly has used Na/EtOH system to desulfonate 2,2-difluoro-1-(4-methylphenyl)-2-(phenylsulfonyl)ethanol in low yield (49%).[5] Inspired by the previous report,[18] we have found that $Na(Hg)/MeOH/Na_2HPO_4$ is a much better desulfonylating system for the *gem*-difluorinated sulfones.[11] In the process of desulfonylation of above-obtained sulfones **3**, sodium/mercury amalgam (10 wt.-% Na in Hg, 5 equiv.) and Na_2HPO_4 (5 equiv., used to control the pH of the solution) in methanol were used, and the reaction was carried out at –20 to –10 °C over a period of 1–3 h. The reactions were monitored by ^{19}F NMR spectroscopy, and quantitative conversions were observed with high selectivity in most cases. The results are summarized in Table 2. Various difluoromethyl alcohols **4** were obtained in good to excellent yields. Both equatorial and axial 4-*tert*-butyl-1-(difluoromethyl)cyclohexanols **4h/4i** and 3-(difluoromethyl)-5α-cholestan-3-ols **4l/4k** were obtained selectively in high yields (see Entries 8, 9, 11, and 12). Interestingly, the reductive desulfonylation reaction condition was found to be also effective for the deacetylation. As a result, 20-(difluoromethyl)pregn-5-ene-3,20-diol (**4m**) was obtained in one step from 20-[difluoro(phenylsulfonyl)methyl]pregn-5-ene-3,20-diol 3-acetate (**3n**) in 93% yield (Table 2, Entry 13). It is worthwhile to mention that in most reactions as shown in Table 2, simple standard work-up is sufficient to give difluoromethyl products **4** with high purity.

Conclusions

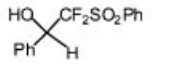
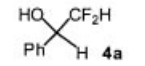
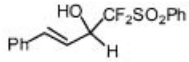
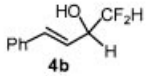
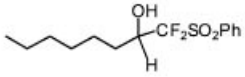
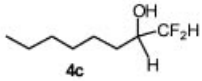
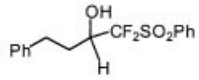
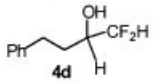
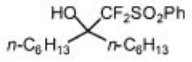
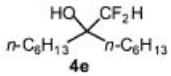
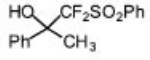
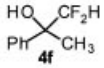
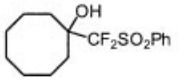
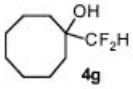
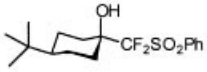
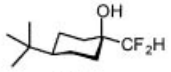
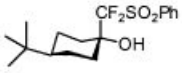
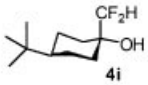
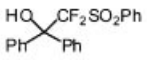
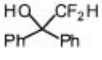
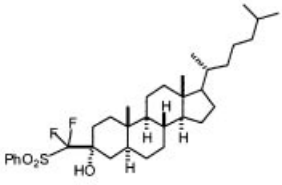
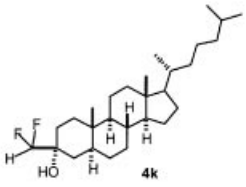
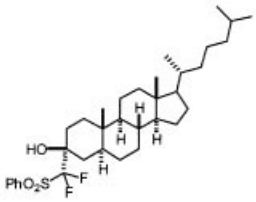
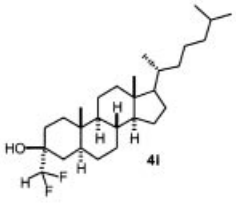
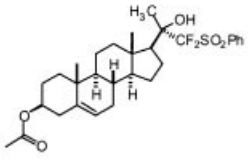
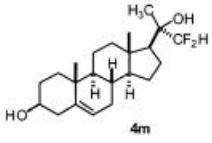
In this communication, we have demonstrated a general and efficient nucleophilic difluoromethylation of carbonyl compounds (both enolizable and non-enolizable aldehydes and ketones) by using a nucleophilic (phenylsulfonyl)difluoromethylation-reductive desulfonylation strategy under mild conditions. Difluoromethyl phenyl sulfone acts as a difluoromethyl anion ("CF_2H^-") equivalent. This method-

Table 1. Nucleophilic reaction of sulfone **1** (1.0 equiv.) with carbonyl compounds **2** (2.0 equiv.) in the presence of LHMDS (2.0 equiv.) in THF/HMPA (10:1 v/v) at –78 °C.

Entry	Carbonyl compound **2**	Reaction time (h)	Product **3**	Yield [%][a]
1		2.0	 **3a**	83
2		2.0	 **3b**	84
3		2.0	 **3c**	65
4		2.0	 **3d**	53
5		1.5	 **3e**	92
6		1.5	 **3f**	83
7		1.5	 **3g**	81
8		3.0	 **3h**	82
9		1.5	 **3i**  **3j**	33 6 8 53
10		3.0	 **3k**	61
11		8.0	 **3l, 3m**	85[b]
12		6.0	 **3n**	81[c]

[a] Isolated yields. [b] Both axial addition product **3l** and equatorial addition product **3m** were obtained in 9:5 ratio. [c] Only one diastereomer was obatined with *de* > 99%.

Table 2. Reductive desulfonylation of carbinols **3** using Na(Hg) amalgam (10 wt.-% Na in Hg, 5 equiv.) and Na_2HPO_4 (5 equiv.) in methanol at –20 to –10 °C.

Entry	Carbinol **3**	Reaction time (h)	Product **4**	Yield [%][a]
1		1.0	 **4a**	79
2		1.5	 **4b**	84
3		2.0	 **4c**	76
4		2.0	 **4d**	86
5		2.0	 **4e**	91
6		1.5	 **4f**	79
7		2.0	 **4g**	88
8		2.0	 **4h**	85
9		2.0	 **4i**	88
10		2.0	 **4j**	82
11		3.0	 **4k**	89
12		3.0	 **4l**	90[b]
13		2.0	 **4m**	93[b]

[a] Isolated yields. [b] 10 wt.-% Na/Hg amalgam (6 equiv.) was applied, and MeOH/THF (1:1) was used as the solvent.

ology requires only inexpensive reagents and standard lab setups, and it promises to be a highly useful synthetic tool for many potential applications. Further elaboration and study of this new difluoromethylation method, including the control of stereoselectivity using modified arylsulfonyl or arylsulfinyl groups, the stereoselectivity with carefully selected (mono- or bicyclic) examples to explore its scope (or limitations), searching for new desulfonylation methods with broader compatibility with other functional groups, and applying this method to other readily enolizable carbonyl compounds, are still under investigations in our labratory.

Experimental Section

General Remarks: Unless otherwise mentioned, all other chemicals were purchased from commercial sources. THF was freshly distilled from sodium. Difluoromethyl phenyl sulfone (**1**) was prepared using known procedures.[7] Silica gel column chromatography was used to isolate the products using 60–200 mesh silica gel (from J. T. Baker), mostly using hexane/ethyl acetate (9:1) as eluent. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on 500 MHz or 400 MHz NMR spectrometer. ^{1}H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ = 0.0 ppm or to the signal of a residual protonated solvent: $CDCl_3$ δ = 7.26 ppm. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ = 0.0 or to the ^{13}C signal of solvent: $CDCl_3$ δ = 77.0 ppm. ^{19}F NMR chemical shifts were determined relative to internal $CFCl_3$ at δ = 0.0. GC-MS data were recorded on a GC-MS spectrometer with a mass selective detector at 70 eV. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI or CI mode.

Typical Procedure for Nucleophilic (Phenylsulfonyl)difluoromethylation of Carbonyl Compounds: A THF solution (3 mL) of $(TMS)_2$-NLi (LHMDS, 334 mg, 2 mmol) was added dropwise to a 50-mL Schlenk flask containing benzaldehyde (212 mg, 2 mmol) and $PhSO_2CF_2H$ (192 mg, 1 mmol) in THF (5 mL)/HMPA (0.5 mL) at –78 °C under N_2. The reaction mixture was then stirred vigorously at –78 °C for 2 h, followed by adding a saturated aq. NaCl solution (10 mL) at this temperature. The solution mixture was extracted with Et_2O (20 mL × 3), and the combined organic phase was dried with $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography to give product **3a** as a white solid, yield 83% (247 mg). ^{1}H NMR ($CDCl_3$): δ = 3.92 (d, J = 4.4 Hz, 1 H), 5.60 (dd, J = 21 Hz, 2.3 Hz, 1 H), 7.36 (m, 3 H), 7.48 (m, 2 H), 7.56 (t, J = 8 Hz, 2 H), 7.70 (t, J = 8 Hz, 1 H), 7.98 (d, J = 8 Hz, 2 H) ppm. ^{19}F NMR ($CDCl_3$): δ = –106.4 (dd, J = 238 Hz, 3 Hz, 1 F), –121.5 (dd, J = 238 Hz, 21 Hz, 1 F) ppm. MS (EI): m/z = 298 [M$^+$], 156, 140, 127, 107, 77. The data are consistent with the previous report.[5]

Typical Procedure for Reductive Desulfonylation: Na/Hg amalgam (10 wt.-% Na in Hg, net sodium content 3 mmol) was added under N_2 into a 50-mL Schlenk flask containing sulfone compound **3a** (149 mg, 0.5 mmol) and Na_2HPO_4 (3 mmol) in 5 mL anhydrous methanol at –20 °C. The reaction mixture was stirred at –20 °C to 0 °C for 1 h. The liquid phase was decanted, and the solid residue was washed with Et_2O. The solids were then treated with elemental sulfur powder to destroy the mercury residue. The solvent of combined organic phase was removed under vacuum, and 20 mL brine was added, followed by extracting with Et_2O brine thrice. The combined ether phase was dried with $MgSO_4$, and the ether was removed to give the crude product, which was further purified by silica gel chromatography to give product **4a** as a colorless liquid, yield 79% (62 mg). ^{1}H NMR ($CDCl_3$): δ = 3.15 (br., 1 H), 4.78 (td, J = 10.2 Hz, 4.7 Hz, 1 H), 5.76 (td, J = 55.6 Hz, 4.7 Hz, 1 H), 7.41 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 73.5 (t, J = 24 Hz), 115.7 (t, J = 246 Hz), 127.1, 128.6, 128.9, 135.8 (t, J = 3.5 Hz) ppm. ^{19}F NMR ($CDCl_3$): δ = –127.7 (ddd, J = 284 Hz, 56 Hz, 9 Hz, 1 F), –128.2 (ddd, J = 284 Hz, 57 Hz, 11 Hz, 1 F) ppm. MS (EI): m/z = 158 [M$^+$], 107, 79, 77. The data are consistent with the previous report.[19]

Supporting Information (see footnote on the first page of this article): Spectroscopic and analytical data of synthesized compounds **3** and **4**.

Acknowledgments

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