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Efficient Nucleophilic Fluoromethylation and Subsequent Transformation of Alkyl and Benzyl Halides Using Fluorobis(phenylsulfonyl)methane

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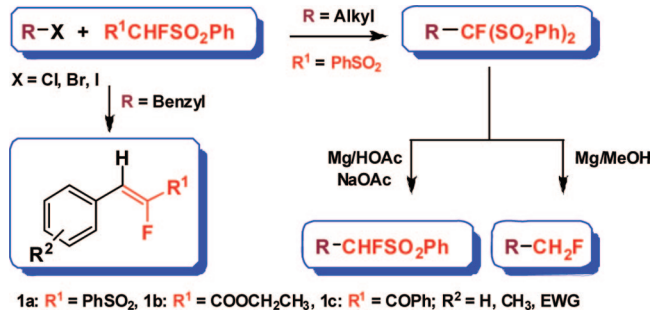
ABSTRACT



An efficient methodology for the nucleophilic fluoromethylation of alkyl and benzyl halides using α-fluoro-α-(phenylsulfonyl)methane (1) as a highly versatile reagent is reported. Using benzyl halides, stereospecific one-pot synthesis of α-fluorovinyl compounds such as α-fluorostyrylsulfones, α-fluorocinnamates, and α-fluorochalcones has been achieved. The methodology has been extended toward the synthesis of α-substituted fluoroalkane derivatives using selective reductive desulfonylation conditions.

The introduction of a monofluoromethyl group into organic molecules has been the subject of numerous articles and has more recently sparked interest in the life sciences.[1] 7α-(Fluoromethyl)dihydroxytestosterone,[2] 3-fluoro-5-(2-(2-(fluoromethyl)thiazol-4-yl)ethynyl)benzonitrile,[3] and 6-(fluoromethyl)purine[4] are a few examples of monofluoromethyl analogues of biologically important compounds synthesized recently. As is already well-known, incorporation of fluorine in drug molecules can highly affect their physicochemical properties such as bond strength, lipophilicity, bioavailability, conformation, electrostatic potential, dipole moment, pK_a, etc.; pharmacokinetic properties such as tissue distribution and rate of metabolism; or pharmacological consequences such as pharmacodynamics and toxicology. In addition, vinyl fluorides play

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an important role in biological sciences as peptidomimics[5] and enzyme inhibitors[6] and are also key synthons for various organic synthetic transformations.[7,8]

Olah and co-workers first reported the use of fluoromethanol[9] for electrophilic monofluoromethylation. The use of fluoromethyl halides, fluoromethyl triflates, and chlorofluoromethane has also been reported.[10] Recently, our group has shown that direct electrophilic monofluoromethylation can be carried out using *S*-(monofluoromethyl)-diarylsulfonium tetrafluoroborate.[1b] Prakash, Shibata, and Hu have independently reported the use of fluorobis(phenylsulfonyl)methane as monofluoromethide equivalent for the transfer of a monofluoromethyl group to alcohols,[1a] allylic acetates,[1c] and epoxides[1d] and also for 1,4-addition reactions to various Michael acceptors.[11] Fluoromethyl phenylsulfone and magnesium benzyl fluoromalonates were also used for nucleophilic monofluoromethylation.[12] Previously, we have reported the use of fluoroiodobis(phenylsulfonyl)methane for radical fluoroalkylations of terminal alkenes.[13] Herein, we disclose a simple and efficient new method for the preparation of terminal monofluorobis(phenylsulfonyl)alkanes (**2a**−**f**) with varying chain lengths from readily available primary halides and their subsequent transformations.

One of the crucial factors for the nucleophilic substitution of primary halides is to match the softness of the nucleophile with that of the electrophilic center. We have previously reported the nucleophilic difluoromethylation of alkyl halides using difluoromethyl phenyl sulfone with potassium *tert*-butoxide as the base.[14] However, we found that using mild bases such as stoichiometric amounts of potassium carbonate in DMF or cesium carbonate in acetonitrile, the soft carbanion [α-fluorobis(phenylsulfonyl)methide] can be generated from α-fluorobis(phenylsulfonyl)methane at room temperature. The reaction proceeds smoothly for both primary alkyl iodides and alkyl bromides to provide the alkylated α-fluoro(phenylsulfonyl)methanes in moderate to excellent yields (Table 1).

Table 1. Nucleophilic Monofluoromethylation of Alkyl Halides Using α-Fluorobis(phenylsulfonyl)methane (**1a**)

entry	starting material	product (**2a**−**j**)	yield (%)[a]
a	$Ph(CH_2)_3I$	$PhCH_2CH_2CH_2CF(SO_2Ph)_2$	83
b	$Ph(CH_2)_4I$	$Ph(CH_2)_4CF(SO_2Ph)_2$	85
c	$CH_3(CH_2)_6I$	$CH_3(CH_2)_6CF(SO_2Ph)_2$	90
d	$CH_3(CH_2)_5I$	$CH_3(CH_2)_5CF(SO_2Ph)_2$	81
e	$PhCH_2Br$	$PhCH_2CF(SO_2Ph)_2$	87
f	$Ph(CH_2)_2Br$	$Ph(CH_2)_2CF(SO_2Ph)_2$	82
g	CH_3CHICH_3	$CH_3CHCF(SO_2Ph)_2CH_3$	60
h	$CH_3CHBr(CH_2)_2CH_3$	$CH_3CH(n\text{-}Pr)CF(SO_2Ph)_2$	40
i	$CH_3(CH_2)_6Cl$	$CH_3(CH_2)_6CF(SO_2Ph)_2$	20[b]
j	$PhCH_2Cl$	$PhCH_2CF(SO_2Ph)_2$	60[c]

[a] Isolated yield. [b] No NaI used. [c] In the presence of NaI.

However, in the case of primary alkyl chlorides, the reaction was found to be sluggish and yield was low. With the addition of a catalytic amount of NaI, the reaction of benzyl chloride provided the desired product in 60% yield. With secondary alkyl iodide (Table 1, entry g), the reaction was found to be rather slow compared to that of primary alkyl iodides.

Interestingly, when the reactions of benzyl halides were carefully examined, formation of fluorovinyl sulfones was observed indicating that a second elimination step occurred after the initial substitution reaction. Vinyl fluorides can be prepared from electrophilic fluorination of vinyllithiums[15,16] or stannanes[17,18] via the Horner−Wadsworth−Emmons condensation of α-fluorophosphonates with carbonyls,[19−21] desulfonylation,[22,23] stannyldesulfonylation,[24−26] silyl and germyldesulfonylation[27,28] of fluorovinyl sulfones, as well as Peterson[29] and Julia[30] olefination. Fluorovinyl sulfones,

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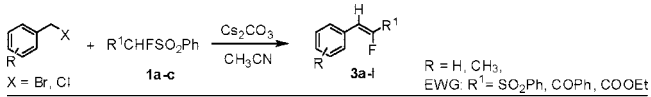
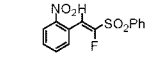
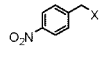
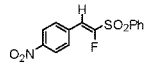
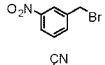
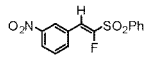
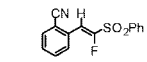
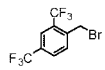
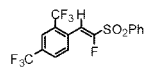
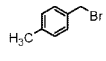
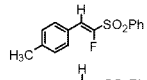
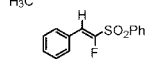
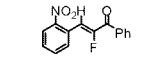
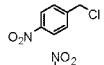
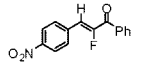
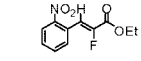
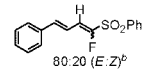
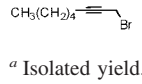
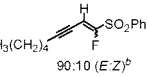
precursors of vinyl fluorides, are commonly synthesized using the Horner−Wittig reaction. In addition, direct alkylation of halides and subsequent elimination using phenylsulfonyl-substituted fluorinated carbanions for the synthesis of fluorovinyl sulfones is quite rare in the literature.[31] We found that when nucleophilic monofluoromethylation of benzyl halides using α-fluorobis(phenylsulfonyl)methane (**1a**) was carried out in the presence of cesium carbonate in acetonitrile, monofluoromethylation followed by subsequent elimination occurs leading to the corresponding fluorovinyl sulfones in moderate to excellent yields (Table 2).

Table 2. Cs_2CO_3/CH_3CN-Catalyzed Synthesis of Fluorovinyl Sulfones and α-Fluoro-α,β-unsaturated Carbonyls



entry	benzyl halide	R^1	temp (°C)	time (h)	product (**3a-l**)	yield (%)[a]
a		SO_2Ph	rt	2		X = Br; 74 X = Cl; 76
b		SO_2Ph	rt	2		X = Br; 87 X = Cl; 78
c		SO_2Ph	70	2		62
d		SO_2Ph	rt	2		85
e		SO_2Ph	rt	2		85
f		SO_2Ph	120	2		62
g		SO_2Ph	120	2		62
h		COPh	80	15		90
i		COPh	100	7		76
j		COOEt	80	15		59
k		SO_2Ph	100	2	 80:20 (*E*:*Z*)[b]	61
l		SO_2Ph	100	2	 90:10 (*E*:*Z*)[b]	56

[a] Isolated yield. [b] Relative ratios determined by ^{19}F NMR.

In all cases, the reaction was found to be highly stereospecific and formation of only the *E*-isomer was observed on the basis of ^{19}F NMR analysis. Benzyl halides with both electron-donating and electron-withdrawing groups on the phenyl ring were tolerated. With electron-withdrawing groups, the yields of the corresponding fluorovinyl sulfones were considerably higher in most cases and the reaction proceeded at room temperature. Electron-rich benzyl systems required heating (120 °C), and the yields were relatively lower (Table 2, entry f). Both substituted benzyl bromides and chlorides work well in this reaction. However, in the case of benzyl chlorides, addition of a small amount of NaI is needed to make the reaction more facile. When we compared the reactivity of *o*-, *m*-, and *p*-nitrobenyl bromides, we found that *ortho*- and *para*-substituted derivatives react immediately to give the corresponding fluorovinyl sulfones in excellent yield. However, the reaction of *m*-nitrobenzyl bromide was sluggish even at 70 °C, resulting in comparably lower yield.

We further extended this methodology to include α-substituted fluoro(phenylsulfonyl)methane derivatives **1b** and **1c** to afford the corresponding α-fluorochalcones and α-fluorocinnamate in one step (Table 2 entries h−j). Unlike in the previous case, the reaction with the α-substituted fluoro(phenylsulfonyl)methane derivatives requires heating. At room temperature, only the S_N2 reaction occurs as manifested by ^{19}F NMR analysis. On heating, the intermediate undergoes elimination to afford the vinyl fluoride as evident by the disappearance of the triplet at −146 ppm and emergence of a doublet at −120 ppm in ^{19}F NMR. (Table 2, entries 3 h−j). With allyl and propargyl bromides the reaction proceeded as expected to give the corresponding products in moderate yields (Table 2, entries k and l). On the other hand, in the case of alkyl halides, the alkylated α-fluoro(phenylsulfonyl)-methane products did not undergo α-eliminations.

The exclusive formation of the *E*-isomer in the benzyl halides (**3a**−**j**) is most likely due to the proximity of the phenyl group. After the initial formation of the benzyl-substituted α-fluoro-α-bis(sulfonyl)methane, the aromatic ring in proximity at the β-position can function as a neighboring group, which assists the exclusive formation of the *E*-isomer. However, in **3k** and **3l**, the effect is less prominent than the other cases and some amount of *Z*-isomer is also formed.

One of the major transformations using sulfone-based organic reactions is its replacement with hydrogen by reductive desulfonylation. Efforts have been directed at developing various reducing agents, including metal amalgams, samarium diiodide, sodium dithionite, hydrides in the presence of transition metal catalysts, and tributyltinhydride (under free radical conditions).[32]

Geminal bis-sulfones are widely used in organic syntheses, as they can be easily deprotonated and used in various nucleophilic substitution and cyclization reactions. One of the challenges involved in this chemistry is the stepwise desulfonylation reaction. Falck and co-workers reported the use of lithium naphthalenide in THF as well as samarium iodide for the reductive monodesulfonylation of *gem*-bis-sulfones.[33]Tuttle et al. reported the use of neutral organic super-electron-donor (S.E.D) reagent for the synthesis of monosulfones from *gem*-disulfones.[34]

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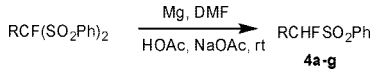
Our aim was to find a system that is more environmentally friendly and economical. We used a Mg/HOAc/NaOAc system for the reductive desulfonylation of the *gem*-disulfones, and to our delight the reaction stopped at monodesulfonylation, enabling us to isolate the products in moderate to excellent yields (Table 3). Hu et al. also reported the use

Table 3. Reductive Monodesulfonylation Using a Mg/HOAc/NaOAc System



entry	starting material	product (**4a**−**g**)	yield (%)[a]
a	$CH_3(CH_2)_5CF(SO_2Ph)_2$	$CH_3(CH_2)_5CHFSO_2Ph$	70
b	$CH_3(CH_2)_6CF(SO_2Ph)_2$	$CH_3(CH_2)_6CHFSO_2Ph$	65
c	$PhCH_2CF(SO_2Ph)_2$	$PhCH_2CHFSO_2Ph$	63
d	$Ph(CH_2)_2CF(SO_2Ph)_2$	$Ph(CH_2)_2CHFSO_2Ph$	65
e	$Ph(CH_2)_3CF(SO_2Ph)_2$	$Ph(CH_2)_3CHFSO_2Ph$	60
f	$Ph(CH_2)_4CF(SO_2Ph)_2$	$Ph(CH_2)_4CHFSO_2Ph$	62
g	$PhO(CH_2)_4CF(SO_2Ph)_2$	$PhO(CH_2)_4CHFSO_2Ph$	63

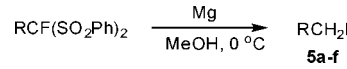
[a] Isolated yield.

of the same system for the reductive desulfonylation of difluoromethyl phenylsulfonyl derivatives.[35]

Inspired by this result, we turned our attention to the reductive di-desulfonylation of α-fluorobis(phenylsulfonyl)-alkanes. Mg/CH_3OH is a well-established reductive desulfonylation system and has been widely exploited in organic synthesis.[32,36]

We have previously reported the use of a Mg/CH_3OH system for the reductive desulfonylation of bis-sulfones for the synthesis of monofluoromethyl-substituted compounds.[1a] Application of this reagent system provided the desired didesulfonylated products in good yields in these cases also (Table 4). Furthermore, under these reaction conditions, we did not detect any monodesulfonylated product.

Table 4. Synthesis of Monoflurомethyl Alkanes Using Mg/MeOH System



entry	starting material	product (**5a**−**f**)	yield (%)[a]
a	$Ph(CH_2)_2CF(SO_2Ph)_2$	$Ph(CH_2)_2CH_2F$	71
b	$Ph(CH_2)_3CF(SO_2Ph)_2$	$Ph(CH_2)_3CH_2F$	48
c	$Ph(CH_2)_4CF(SO_2Ph)_2$	$Ph(CH_2)_4CH_2F$	56
d	$Ph(CH_2)_5CF(SO_2Ph)_2$	$Ph(CH_2)_5CH_2F$	75
e	$PhO(CH_2)_3CF(SO_2Ph)_2$	$PhO(CH_2)_3CH_2F$	83
f	$PhO(CH_2)_4CF(SO_2Ph)_2$	$PhO(CH_2)_4CH_2F$	77

[a] Isolated yield.

In conclusion, we have developed an efficient methodology for the synthesis of alkyl(benzyl) α-fluoro-α-bis(phenylsulfonyl)methanes by nucleophilic substitution of the corresponding alkyl/benzyl halides with α-fluorobis(phenylsulfonyl)methane (**1a**). We have also developed an efficient one-pot stereospecific synthesis of fluorovinyl sulfones. By using different α-substituted fluoro(phenylsulfonyl)methane derivatives, a variety of vinyl fluorides (**3a**−**l**) can be obtained. With proper choice of reductive desulfonylating reagent system, we were also able to perform the stepwise desulfonylation reaction to yield the α-fluoro-α-(phenylsulfonyl)-alkanes (**4a**−**g**) and α-fluoroalkanes (**5a**−**f**), respectively.

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Supporting Information Available: General experimental procedure and spectroscopic data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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