Fluorinated Alkenes

Difluoromethyl Phenyl Sulfone, a Difluoromethylidene Equivalent: Use in the Synthesis of 1,1-Difluoro-1-alkenes**

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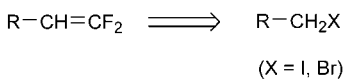
1,1-Difluoro-1-alkenes are unique compounds with unusually high electrophilicity from the *gem*-difluorovinyl group, and recently have drawn many synthetic and theoretical endeavors.[1] *gem*-Difluorovinyl functionality has been known to act as a bioisostere for aldehydes and ketones,[2] and it is critical to many biologically active molecules such as enzyme inhibitors[1,3] and pesticides.[4] 1,1-Difluoro-1-alkenes are also useful synthetic precursors for the preparation of other fluorinated compounds and polymers.[5] Although several different methods for the preparation of 1,1-difluoro-1-alkenes have been disclosed in the literature including the Wittig reaction using difluoromethylene ylides,[6] we now report an efficient method for the transformation of readily available primary alkyl halides into 1,1-difluoro-1-alkenes (Scheme 1).



Scheme 1. Preparation of 1,1-difluoro-1-alkenes from primary alkyl halides.

One can envision a nucleophilic substitution–elimination strategy for this transformation, that is, a fluorine-bearing nucleophile (such as CF_3^-) substitutes the halogen atom of the alkyl halide followed by an α,β-elimination (−HF or others). However, while alkyl halides can readily react with various carbon nucleophiles (mostly by S_N2 reactions) to form carbon–carbon bonds, their nucleophilic substitution reactions with fluorine-bearing carbon nucleophiles are generally difficult due to their unmatched hard–soft nature.[7] In addition, although fluorinated organocopper reagents (R_fCu) can be used to couple with aryl, vinyl, benzyl, and allyl halides, their reactions with simple alkyl halides are not effective.[8]

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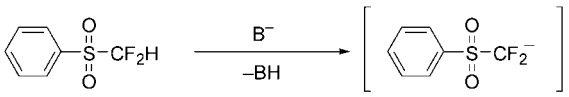
The possible solution to this problem is to introduce a proper auxiliary functional group connecting to the fluorinated carbon nucleophile to increase its softness, since the alkyl halide is a soft electrophile. Furthermore, the proper auxiliary group should be easily removed or transformed into other functional groups afterwards. The benzenesulfonyl group ($PhSO_2$) is one of the choices, for its softness and its varying chemical reactivities (so-called "chemical chameleon").[9] Difluoromethyl phenyl sulfone (**1**) is the ideal compound for this purpose, due to its easy generation of the (benzenesulfonyl)difluoromethyl anion **2** after the deprotonation of its CF_2H group (Scheme 2).[10] Difluoromethyl phenyl sulfone can be readily prepared from sodium thiophenoxide and chlorodifluoromethane followed by oxidation.[10,11] The nucleophilic addition of **1** with carbonyl compounds in the presence of a base has been demonstrated.[10b,c] Recently, we have reported the synthetic application of **1** as a difluoromethyl anion equivalent ("CF_2H^-")[12] as well as a selective difluoromethylene dianion equivalent ("$^-CF_2^-$").[10c] Herein, we disclose another significant synthetic application of **1** as a difluoromethylidene equivalent ("$=CF_2$"), which enables a novel synthesis of 1,1-difluoro-1-alkenes from primary alkyl halides using an unprecedented nucleophilic substitution–elimination approach.

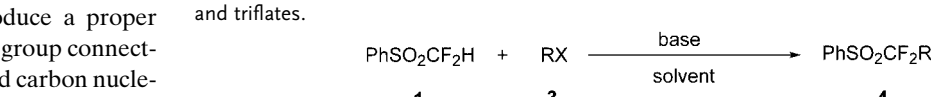


1 **2**

Scheme 2. Generation of (benzenesulfonyl)difluoromethide from difluoromethyl phenyl sulfone and a base.

The nucleophilic substitution of difluoromethyl phenyl sulfone **1** with alkyl bromides, alkyl iodides, and alkyl triflates were examined, to produce alkylated difluoromethyl sulfone **3**, with careful modifications of the reaction conditions (Table 1). The reactions were typically performed under an argon atmosphere, and a base was added to a mixture of **1** and **3**. The best product yield was obtained when one equivalent of **1** was treated with four equivalents of primary alkyl iodide and two equivalents of *t*BuOK as a base in DMF at −50 °C for 1 h (Table 1, run 5). Primary alkyl bromides are also suitable for the reaction but with somewhat lower yields (Table 1, runs 1–4). A secondary alkyl halide, however, did not give the anticipated product (Table 1, run 9), indicating that the reaction proceeds by a typical S_N2 pathway. Methyl triflate did not react with **1** either to give the expected product (Table 1, runs 10, 11), which may be due to the fast reaction between DMF, alkyl triflate, and *t*BuOK to form the dialkyl acetal of DMF.[13]

Table 1: Optimization of the reaction conditions for the nucleophilic substitution of **1** with alkyl halides and triflates.



1 **3** **4**

Run	**1** (equiv)	**3** (equiv)	Base (equiv)	Solvent	*T* [°C]	*t* [h]	Yield of **4** [%][a]
1	1.0	*n*-$C_5H_{11}Br$ (2.1)	*t*BuOK (1.0)	DMF	−50–25	1.0	34
2	1.0	*n*-$C_5H_{11}Br$ (2.1)	*t*BuOK (1.0)	DMF	−50–25	16.0	29
3	1.0	*n*-$C_5H_{11}Br$ (2.1)	*t*BuOK (2.0)	DMF	−50–25	1.0	52
4	1.0	*n*-$C_5H_{11}Br$ (4.0)	*t*BuOK (2.0)	DMF	−50	1.0	61
5	1.0	*n*-$C_5H_{11}I$ (4.0)	*t*BuOK (2.0)	DMF	−50	1.0	85
6	1.0	*n*-$C_5H_{11}Br$ (10.0)	NaOH (25.0)[b]	CH_2Cl_2	25	20.0	0[c]
7	1.0	*n*-C_2H_5I (4.0)	*t*BuOK (2.0)	DMF	−50	1.0	65
8	1.0	*n*-C_2H_5I (4.0)	*t*BuOK (2.0)	THF	−50	1.0	0[d]
9	1.0	2-iodobutane (4.0)	*t*BuOK (2.0)	DMF	−50	1.0	0[d]
10	1.0	$CF_3SO_3CH_3$ (4.0)	*t*BuOK (2.0)	DMF	−50	1.0	0[e]
11	1.0	$CF_3SO_3CH_3$ (4.0)	*t*BuOK (2.0)	THF	−50	1.0	0[e]

[a] Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] 50 wt% aqueous NaOH solution was used, with the catalytic amount of phase-transfer agent Aliquat 336. [c] Unreacted **1** and a small amount of the by-product $PhSO_2CF_2SPh$ were observed. [d] A messy product mixture was observed. [e] Starting material **1** was recovered.

Following optimization of the reaction conditions, a variety of alkyl-substituted *gem*-difluoromethyl phenyl sulfones **4** were prepared in good yields (Table 2). Various primary alkyl iodides with different chain lengths were able to be substituted with (benzenesulfonyl)difluoromethide (in situ generated from **1)** and *t*BuOK (Table 2, entries 1–6). Substituted alkyl iodides also behave in the similar way, which leads to the formation of structurally diverse *gem*-difluorinated sulfones (Table 2, entries 7–12). Alkyl-substituted difluoromethyl sulfones themselves are a group of useful compounds used as nonlinear optical materials.[14] The known available method for their preparation is by the α-fluorination of sulfoxides bearing α-hydrogen atoms by elemental fluorine

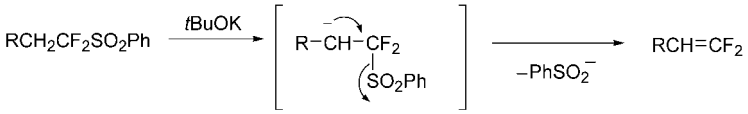
Table 2: Preparation of substituted difluoromethyl sufones **4** from **1** (1 equiv), alkyl iodides (4 equiv), and *t*BuOK (2 equiv) in DMF at −50 °C for 1 h.

Entry	RCH_2I	$RCH_2CF_2SO_2Ph$ (**4**)	Yield [%][a]
1	$CH_3(CH_2)_6I$	$CH_3(CH_2)_6CF_2SO_2Ph$ (**4a**)	79
2	$CH_3(CH_2)_4I$	$CH_3(CH_2)_4CF_2SO_2Ph$ (**4b**)	80
3	$CH_3(CH_2)_3I$	$CH_3(CH_2)_3CF_2SO_2Ph$ (**4c**)	84
4	$CH_3(CH_2)_2I$	$CH_3(CH_2)_2CF_2SO_2Ph$ (**4d**)	73
5	CH_3CH_2I	$CH_3CH_2CF_2SO_2Ph$ (**4e**)	62
6	CH_3I	$CH_3CF_2SO_2Ph$ (**4f**)	42
7	$Ph(CH_2)_3I$	$Ph(CH_2)_3CF_2SO_2Ph$ (**4g**)	71
8	$Ph(CH_2)_4I$	$Ph(CH_2)_4CF_2SO_2Ph$ (**4h**)	52
9	$Ph(CH_2)_5I$	$Ph(CH_2)_5CF_2SO_2Ph$ (**4i**)	59
10	$Ph(CH_2)_6I$	$Ph(CH_2)_6CF_2SO_2Ph$ (**4j**)	50
11	$Ph_2CH(CH_2)_2I$	$Ph_2CH(CH_2)_2CF_2SO_2Ph$ (**4k**)	37
12	$PhO(CH_2)_3I$	$PhO(CH_2)_3CF_2SO_2Ph$ (**4l**)	71
13	$PhO(CH_2)_4I$	$PhO(CH_2)_4CF_2SO_2Ph$ (**4m**)	60

[a] Yield of isolated product.

with low yields (10–20%).[15] Our current methodology possesses many advantages such as convenience, safety, cost, and efficiency.

During the preparation of alkyl-substituted difluoromethyl sulfones **4**, the formation of a small amount of 1,1-difluoro-1-alkenes as by-products was observed. This is due to the high acidity of the α-hydrogen atom of the difluoromethylene group, which allows the easy deprotonation by *t*BuOK to generate a new carbanion species **5** (Scheme 3). Intermediates **5** readily undergo β-elimination to eliminate the benzenesulfonyl group (rather than a fluorine atom) to afford 1,1-difluoro-1-alkenes **6**. The benzenesulfonyl group is



Scheme 3. The formation of 1,1-difluoro-1-alkenes.

known to be a better leaving group than a fluoride.[9a] Hence, we readily prepared 1,1-difluoro-1-alkenes **6** from the isolated substitution product **4** with *t*BuOK in THF at −20 °C to ambient temperature. The deprotonation/β-elimination reactions proceeded rapidly (within 1 h). Various 1,1-difluoro-1-alkenes were prepared in good to excellent yields by this method using the previously prepared sulfone compounds **4** (Table 3). Thus, the primary alkyl iodides were transformed

Table 3: Preparation of 1,1-difluoro-1-alkenes **6** by deprotonation–elimination reactions using **4** and *t*BuOK in THF at temperatures ranging from −20 °C to room temperature.

Entry	$RCH_2CF_2SO_2Ph$ (**4**)	$RCH{=}CF_2$ (**6**)	Yield [%][a]
1	$Ph(CH_2)_3CF_2SO_2Ph$	$Ph(CH_2)_2CH{=}CF_2$ (**6a**)	85
2	$Ph(CH_2)_4CF_2SO_2Ph$	$Ph(CH_2)_3CH{=}CF_2$ (**6b**)	71
3	$Ph(CH_2)_5CF_2SO_2Ph$	$Ph(CH_2)_4CH{=}CF_2$ (**6c**)	82
4	$Ph(CH_2)_6CF_2SO_2Ph$	$Ph(CH_2)_5CH{=}CF_2$ (**6d**)	80
5	$Ph_2CH(CH_2)_2CF_2SO_2Ph$	$Ph_2CHCH_2CH{=}CF_2$ (**6e**)	84
6	*p*-MeO-C_6H_4-$(CH_2)_4CF_2SO_2Ph$	*p*-MeO-C_6H_4-$(CH_2)_3CH{=}CF_2$ (**6f**)	55
7	$PhO(CH_2)_3CF_2SO_2Ph$	$PhO(CH_2)_2CH{=}CF_2$ (**6g**)	88
8	$PhO(CH_2)_4CF_2SO_2Ph$	$PhO(CH_2)_3CH{=}CF_2$ (**6h**)	87

[a] Yield of isolated product.

into 1,1-difluoro-1-alkenes in two steps by a substitution–elimination sequence. The advantage of this method is that the reactions are facile and straightforward, and necessitate only safe and inexpensive reagents and simple experimental procedures.

In conclusion, the unprecedented nucleophilic substitution reactions (S_N2) of (benzenesulfonyl)difluoromethide (generated in situ from difluoromethyl phenyl sulfone and a base) with primary alkyl halides (preferentially primary alkyl iodides) have been developed, which demonstrates the efficient carbon–carbon bond formation between a fluorinated carbanion and primary alkyl halides. The new alkyl-substitued difluoromethyl sulfones are highly efficient in their facile transformations into 1,1-difluoro-1-alkenes by base-induced eliminations. Difluoromethyl phenyl sulfone acts as a difluoromethylidene equivalent. This new methodology promises to be a highly useful synthetic tool for many other potential applications.

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