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Nucleophilic Difluoromethylation of Primary Alkyl Halides Using Difluoromethyl Phenyl Sulfone as a Difluoromethyl Anion Equivalent

G. K. Surya Prakash,* Jinbo Hu, Ying Wang, and George A. Olah

Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661

gprakash@usc.edu

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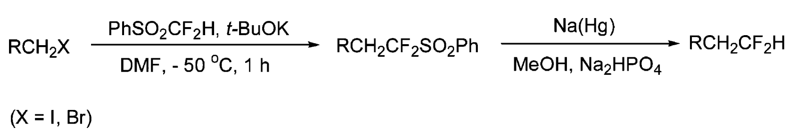
ABSTRACT



A facile and efficient nucleophilic difluoromethylation of primary alkyl halides has been disclosed through a novel nucleophilic substitution–reductive desulfonylation strategy, using difluoromethyl phenyl sulfone as a difluoromethyl anion (“CF_2H^-”) equivalent.

Selective introduction of difluoromethyl group (CF_2H) into organic molecules is of great importance due to its ability to contribute special biological properties to those molecules. CF_2H functionality has been known to be isosteric and isopolar to hydroxyl (OH) group and behaves as a hydrogen donor through hydrogen bonding.[1−5] Moreover, CF_2H group has similar high lipophilicity as the trifluoromethyl group, which is useful in applications where a more lipophilic hydrogen bond donor other than OH is required.[3] As a result, CF_2H group has been frequently incorporated into various biologically active compounds (such as enzyme inhibitors,[6] sugars,[7] pesticides,[8] and herbicides[9]) and materials (such as liquid crystals[10] and fluoropolymers[11]). Many CF_2H-containing compounds have also been used as anesthetics, including well-known desflurane and isoflurane.[12]

Several methods have been developed for the preparation of CF_2H-containing compounds, including the deoxofluorination of aldehydes using SF_4, DAST, or SeF_4,[13] nucleophilic fluorination of *gem*-bistriflates using TBAF,[14] fluorination of 1,2- or 1,3-dithianes using BrF_3 and other in situ-generated halogen fluorides,[5,15] addition of CF_2Br_2 into double bonds,[16]

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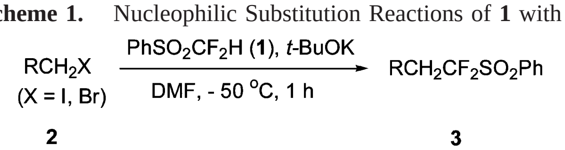
$S_{RN}1$ reaction between a nucleophile and CF_2HCl,[17] and hydrogenation of terminal 1,1-difluoroalkenes.[18] Nucleophilic introduction of a CF_2H building block into carbonyl compounds has been reported, using (difluoromethyl)dimethylphenylsilane,[19] (chlorodifluoromethyl)trimethylsilane,[3] or difluoromethyl phenyl sulfone[20] as the CF_2H precursor. Previously, we have reported the preparation of difluoromethylsilanes via the magnesium metal-mediated reductive difluoromethylation of chlorotrialkylsilanes using difluoromethyl phenyl sulfone.[21] Herein, we would like to disclose a simple and efficient new method for the preparation of difluoromethyl compounds from readily available primary alkyl halides using difluoromethyl phenyl sulfone[22] (**1**) as a CF_2H precursor.

The nucleophilic substitution reactions between difluoromethyl anion ("CF_2H^-", commonly generated in situ) and simple alkyl halides are generally difficult due to the unmatched hard−softness.[23] Recently, we have succeeded in the S_N2 reactions between (benzenesulfonyl)difluoromethyl anion (generated in situ from **1** and a base) and primary alkyl halides (preferably iodides) (see Scheme 1), which enabled

Scheme 1. Nucleophilic Substitution Reactions of **1** with **2**



us to synthesize 1,1-difluoroalkenes from primary alkyl halides in substitution−elimination mode.[24] As shown in Table 1, a variety of alkyl-substituted *gem*-difluoromethyl phenyl sulfones **3** were prepared in good yields using difluoromethyl sulfone **1** (1 equiv), primary alkyl iodides or bromides (4 equiv), and *t*-BuOK (2 equiv) at −50 °C for about 1 h.[24]

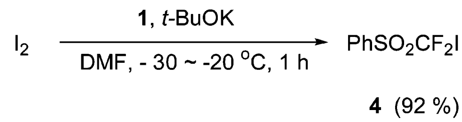
It is worthwhile to mention that the similar nucleophilic substitution reaction between the in situ-generated (benzenesulfonyl)difluoromethyl anion (from **1** and *t*-BuOK) and other electrophiles worked equally well. When excess elemental iodine was used as the electrophile, $PhSO_2CF_2I$ (**4**) was produced in 92% yield (Scheme 2). Interestingly,

Table 1. Preparation of Fluorinated Sulfones **3** from Primary Alkyl Halides **2**, Difluoromethyl Sulfone **1**, and *t*-BuOK in DMF at − 50 °C for 1 h

entry	RCH_2X (**2**)	$RCH_2CF_2SO_2Ph$ (**3**)	yield (%)[a]
1	$CH_3(CH_2)_6I$	$CH_3(CH_2)_6CF_2SO_2Ph$ (**3a**)	79
2	$CH_3(CH_2)_4I$	$CH_3(CH_2)_4CF_2SO_2Ph$ (**3b**)	80
3	$CH_3(CH_2)_4Br$	$CH_3(CH_2)_4CF_2SO_2Ph$ (**3b**)	61
4	$CH_3(CH_2)_3I$	$CH_3(CH_2)_3CF_2SO_2Ph$ (**3c**)	84
5	$CH_3(CH_2)_2I$	$CH_3(CH_2)_2CF_2SO_2Ph$ (**3d**)	73
6	$Ph(CH_2)_3I$	$Ph(CH_2)_3CF_2SO_2Ph$ (**3e**)	71
7	$Ph(CH_2)_4I$	$Ph(CH_2)_4CF_2SO_2Ph$ (**3f**)	52
8	$Ph(CH_2)_5I$	$Ph(CH_2)_5CF_2SO_2Ph$ (**3g**)	59
9	$Ph(CH_2)_6I$	$Ph(CH_2)_6CF_2SO_2Ph$ (**3h**)	50
10	$Ph_2CH(CH_2)_2I$	$Ph_2CH(CH_2)_2CF_2SO_2Ph$ (**3i**)	37
11	$PhO(CH_2)_3I$	$PhO(CH_2)_3CF_2SO_2Ph$ (**3j**)	71
12	$PhO(CH_2)_4I$	$PhO(CH_2)_4CF_2SO_2Ph$ (**3k**)	60

[a] Isolated yield.

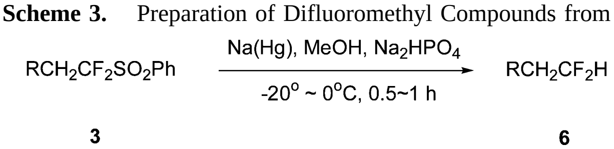
Scheme 2. Nucleophilic Substitution Reaction of **1** with I_2



when *n*-perfluorohexyl iodide was applied instead of I_2, the same product **4** was produced in 39% yield. Difluoromethyl phenyl sulfoxide, $PhSOCF_2H$, also reacts with *n*-butyl iodide in the presence of *t*-BuOK, to give 1,1-difluoropentyl phenyl sulfoxide (**5**) in 54% yield.

Reductive desulfonylation is widely used in the organic synthesis in order to remove the arenesulfonyl groups after the desired transformations.[25] After the desulfonylation, the arenesulfonyl groups are commonly replaced by a hydrogen atom. Reductive desulfonylations of *gem*-difluorinated sulfones are scarce. (Benzenesulfonyl)difluoromethyl carbinols have been reductively desulfonylated into difluoromethyl carbinols in low yields, using sodium metal in ethanol.[20a] Similar poor yields were obtained when we tried a Na/MeOH system as a desulfonylating agent for the alkylated difluoromethyl sulfones **3**. It soon became apparent that under the reaction conditions, the in situ-generated strong base MeONa will further complicate the reaction and thus decrease the desulfonylation efficiency. Inspired by the early report that the clean desulfonylation reaction can be obtained by applying a buffering agent to control the pH,[26] we added sodium monohydrogenphosphate (Na_2HPO_4) in our desulfonylation reactions in order to selectively produce difluoromethylated products (see Scheme 3). Sodium/mercury amal-

Scheme 3. Preparation of Difluoromethyl Compounds from **3**



gam (5 wt % Na in Hg) was used, and the reactions were carried out at − 20 to 0 °C for 0.5−1 h. Various difluo-

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Table 2. Preparation of Difluoromethyl Compounds **6** by Desulfonylations of **3** Using Na(Hg)/MeOH/Na_2HPO_4 at Temperatures between − 20 and 0 °C

entry	$RCH_2CF_2SO_2Ph$ (**3**)	RCH_2CF_2H (**6**)	yield (%)[a]
1	$Ph(CH_2)_4CF_2SO_2Ph$	$Ph(CH_2)_4CF_2H$ (**6a**)	87
2	$Ph(CH_2)_5CF_2SO_2Ph$	$Ph(CH_2)_5CF_2H$ (**6b**)	90
3	$Ph(CH_2)_6CF_2SO_2Ph$	$Ph(CH_2)_6CF_2H$ (**6c**)	85
4	$Ph_2CH(CH_2)_2CF_2SO_2Ph$	$Ph_2CH(CH_2)_2CF_2H$ (**6a**)	89
5	*p*-MeO-C_6H_4-$(CH_2)_4CF_2$-SO_2Ph	*p*-MeO-C_6H_4-$(CH_2)_4CF_2H$ (**6e**)	80
6	$PhO(CH_2)_3CF_2SO_2Ph$	$PhO(CH_2)_3CF_2H$ (**6f**)	91
7	$PhO(CH_2)_4CF_2SO_2Ph$	$PhO(CH_2)_4CF_2H$ (**6g**)	88

[a] Isolated yield.

romethyl compounds **6** were obtained from the corresponding alkylated difluoromethyl sulfones **3** in excellent yields (see Table 2).[27] The reactions were highly selective, which simplified the final purification processes.

In conclusion, the substitution of the halogen atom of a primary alkyl halide (preferably alkyl iodide) by a CF_2H group has been achieved, using a nucleophilic substitution−reductive desulfonylation strategy. Difluoromethyl phenyl sulfone (**1**) acts as a difluoromethyl anion ("CF_2H^-") equivalent. This new synthetic methodology possesses many advantages, including convenience, cost, and efficiency, and promises to be a highly useful synthetic tool for many other potential applications.

Acknowledgment. Support of our work in part by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

Supporting Information Available: General experimental paragraph; experimental procedures for the preparation of **3**, **4** and **6**; and ^1H, ^{19}F, ^{13}C NMR, and mass characterization data of the isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Difluoromethyl phenyl sulfone can be readily prepared from PhSNa and CF_2HCl followed by simple oxidation. See refs 17 and 20.

(23) Nucleophilic substitution reactions between CF_2H^- (generated in situ from Et_3SiCF_2H and KF in DMF at 100 °C) and simple alkyl halides have been attempted by us with no success. The CuI-mediated coupling reaction between iodobenzene and CF_2H^- (generated similarly) did not work either.

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(27) Desulfonylation reaction works equally well for all the sulfones **3** as shown in Table 1. The compounds chosen as examples for Table 2 contain aromatic moieties since they are less volatile and are easily isolated.