JOC*Note*

Radical (Phenylsulfonyl)difluoromethylation with Iododifluoromethyl Phenyl Sulfone

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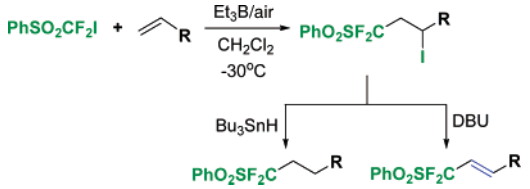

An unprecedented radical (phenylsulfonyl)difluoromethylation of terminal alkenes with $PhSO_2CF_2I$ has been achieved by using Et_3B/air as an initiator. This synthetic methodology was also used in the one-pot regioselective preparation of $PhSO_2CF_2$-substituted alkanes, and in the regio- and stereoselective preparation of $PhSO_2CF_2$-substituted alkenes with high *E*/*Z* ratio (up to ≥100:1).

Recently, fluorine has been highlighted as a fabulous element for life sciences-related applications.[1] It is well-known that the incorporation of one or just a few fluorine atom(s) into organic molecules can often have profound effects on their bioactivities, and as a result, a significant portion of agrochemicals and pharmaceuticals on the market contain fluorine.[1−3] Fluorination and fluoroalkylation are the two major synthetic methods to prepare partially fluorinated organic compounds. In the selective fluoroalkylation arena, while nucleophilic, electrophilic, and radical trifluoromethylations have been extensively studied over the past 30 years, the systematic exploration of the analogous difluoromethylation and difluoromethylenation has emerged more recently.[2] In this context, there is an increasing interest in developing efficient synthetic methods for selective introduction of (phenylsulfonyl)difluoromethyl group ($PhSO_2CF_2$) into organic molecules, based on the fact that the $PhSO_2CF_2$ group is a versatile functionality that can be readily converted to other highly useful difluorinated moieties such as difluoromethyl (CF_2H) and difluoromethylene ($-CF_2-$ or $=CF_2$) groups.[4−6] The known methods for directly introducing $PhSO_2CF_2$ group are all based on nucleophilic reactions with the $PhSO_2CF_2^-$ anion, which is commonly derived from $PhSO_2CF_2H$, $PhSO_2CF_2SiMe_3$, or $PhSO_2CF_2Br$ reagents.[4−6] However, we are not aware of any reports of either radical (phenylsulfonyl)difluoromethylation or the (phenylsulfonyl)difluoromethyl radical ($PhSO_2CF_2^{\bullet}$) itself. As our continuing effort in developing selective difluoromethylation and difluoromethylenation methodologies,[4] we have been seeking new approaches of transferring $PhSO_2CF_2$ group under neutral reaction conditions that tolerate more sensitive functional groups. In this note, we report our recent success in the generation of (phenylsulfonyl)difluoromethyl radical species ($PhSO_2CF_2^{\bullet}$) and its use in the radical (phenylsulfonyl)difluoromethylation of alkenes.

Taking advantage of the simple preparation of iododifluoromethyl phenyl sulfone ($PhSO_2CF_2I$, **1**),[7] we chose compound **1** as the (phenylsulfonyl)difluoromethyl radical precursor. By using 1-hexene (**2a**) as a model compound, we examined the radical atom transfer reaction between **1** and **2a** (Table 1). After trying several radical initiators, we found that copper powder (Cu^0), $Pd(PPh_3)_4$, and $Na_2S_2O_4$ are not suitable for the reaction (entries 1−3), which is surprisingly different from other known radical polyfluoroalkylation reactions.[8] Nevertheless, we found that Et_3B/air[9] was an efficient initiating system for the present radical atom transfer process between **1** and **2a** (Table 1, entries 4−13). To ensure a high conversion of reagent **1** in the reaction, 1.0 equiv of Et_3B was used for all cases. Furthermore, while

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(7) Compound **1** can be readily prepared from $PhSO_2CF_2H$ and I_2 in the presence of ^{t}BuOK in 92−95% isolated yields. See: Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Org. Lett.* **2004**, *6*, 4315−4317.

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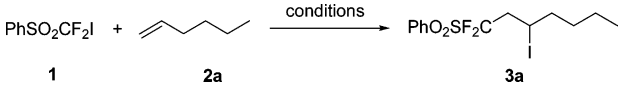
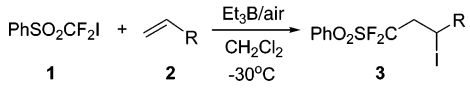
TABLE 1. Survey of Reaction Conditions



entry	initiator (equiv)[a]	molar ratio (**1**:**2a**)	solvent	temperature (°C)	concentration (mol/L)[b]	yield (%)[c]
1	Cu (0.5)	1:2.0	DMF	55	0.20	0
2	$Pd(PPh_3)_4$ (0.03)	1:2.0	benzene	60	0.20	5[d]
3	$Na_2S_2O_4$ (1.5)	1:2.0	CH_3CN/H_2O	24	0.50	—[e]
4	Et_3B (1.0)/air	1:2.0	benzene	24	0.15	56
5	Et_3B (1.0)/air	1:2.0	benzene	0	0.15	69
6	Et_3B (1.0)/air	1:1.3	benzene	0	0.15	56
7	Et_3B (1.0)/air	1:2.0	benzene	0	0.25	70
8	Et_3B (1.0)/air	1:2.0	toluene	0	0.15	55
9	Et_3B (1.0)/air	1:2.0	CH_2Cl_2	0	0.15	70
10	Et_3B (1.0)/air	1:2.0	THF	0	0.15	68
11	Et_3B (1.0)/air	1:2.0	CH_2Cl_2	−30	0.15	75
12	Et_3B (1.0)/air	1:2.0	CH_2Cl_2	−78	0.15	56
13	Et_3B (1.0)/air	1:2.0	THF	−78	0.15	46

[a] The molar equivalent of the initiator was calculated relative to the amount of compound **1**. [b] The concentration of **1** in the reaction mixture before an initiator was added. [c] Isolated yield. [d] Determined by ^{19}F NMR spectroscopy. [e] A complex product mixture was obtained.

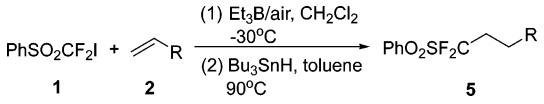
TABLE 2. Et_3B-Initiated Radical Atom Transfer Reactions between 1 and Alkenes 2



entry	R	product	yield (%)[a]
1	1-butyl	**3a**	75
2	1-decyl	**3b**	72
3	trimethylsilyl	**3c**	71
4	$CH_3C(O)CH_2CH_2$–	**3d**	70
5	$EtOC(O)CH_2CH_2CH_2$–	**3e**	78
6	$HO_2CCH_2CH_2$–	**3f**	73
7	$HOCH_2$–	**3g**	64
8	*p*-$CH_3OC_6H_4OCH_2$–	**3h**	56

[a] Isolated yield.

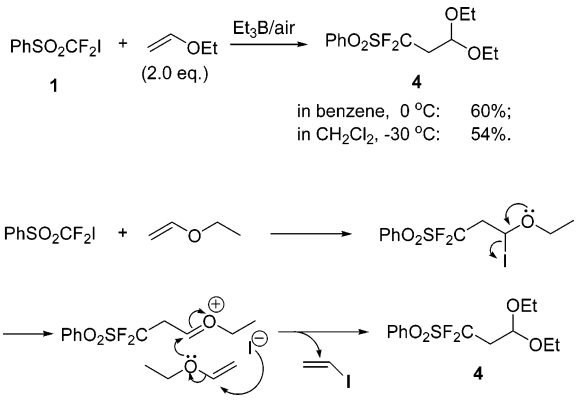
TABLE 3. One-Pot (Phenylsulfonyl)difluoromethylation of Alkenes 2



entry	R	product	yield (%)[a]
1	1-butyl	**5a**	75
2	1-decyl	**5b**	70
3	trimethylsilyl	**5c**	65
4	$CH_3C(O)CH_2CH_2$–	**5d**	69
5	$EtOC(O)CH_2CH_2CH_2$–	**5e**	78
6	*p*-$CH_3OC_6H_4OCH_2$–	**5f**	57

[a] Isolated yield.

SCHEME 1. Preparation of Compound 4 and Proposed Mechanism



solvents and reactant concentration did not exhibit a significant effect, the reaction temperature played an important role in the reaction (entries 4−13). The best yield (75%) was obtained when the reaction was carried out in CH_2Cl_2 at −30 °C (entry 11).

By using this optimized reaction condition, we studied the scope of the Et_3B/air-initiated radical reactions between the new (phenylsulfonyl)difluoromethylating reagent **1** and a variety of structurally diverse terminal alkenes. In all cases as shown in Table 2, the reactions proceeded smoothly to give the regioselective products **3a**−**3h** in satisfactory to good yields, with the reaction being compatible with different functionalities such as carbonyl, ester, carboxylic acid, ether, and hydroxyl groups. It is interesting that the reaction between **1** and vinyl ethyl ether gave the acetal **4** as the product (Scheme 1), possibly via an oxonium ion intermediate (see proposed mechanism in Scheme 1).

It has been reported that $Zn/NiCl_2$ can be used as a mild and efficient reagent for the one-pot addition/reductive de-iodination reactions between polyfluoroalkyl iodides and terminal alkenes.[10] However, we found that when $Zn/NiCl_2$ reagent was applied in the reaction between **1** and **2a**, the reaction was sluggish. We then used a one-pot two-step procedure to accomplish a clean (phenylsulfonyl)difluoromethylation of alkenes with **1** by adding the Et_3B/air to initiate the addition reaction to give intermediate **3**, followed by adding Bu_3SnH reagents to facilitate the de-iodination reaction (see Table 3). The reactions proceed smoothly to give the (phenylsulfonyl)-difluoromethylated alkanes in 57−78% isolated yields, with good toleration of several types of functional groups. This one-pot approach is a good alternative for the previously reported

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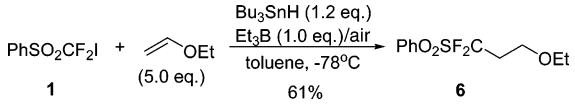
SCHEME 2. Preparation of Compound 6



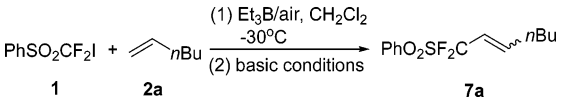
preparative method for product **5** under strong basic conditions.[5c,d] Furthermore, this reaction also worked for vinyl ethyl ethers (Scheme 2). In the presence of Bu_3SnH and Et_3B/air, the reaction between **1** and excess amount of vinyl ethyl ether (5 equiv) in toluene at −78 °C gave the corresponding product **6** in 61% isolated yield (in this case, the formation of acetal **4** was not observed).

With the expectation that the intermediate compounds **3** can also undergo base-mediated dehydroiodination to give (phenylsulfonyl)difluoromethylated alkenes, we carried out a one-pot preparation of fluoroalkylated alkenes from **1** and terminal alkenes **2**. First, we scanned the reaction conditions by using 1-hexene (**2a**) as a model compound, and the results are shown in Table 4. It was found that triethyl amine was unable to dehydroiodinate the intermediate product **3a** (entries 1 and 2). In polar solvent, inorganic base such as K_2CO_3 and KOH can promote the reaction, but only moderate *E*/*Z* isomeric ratios were observed (entries 3−5). 1,5-Diazabicyclo[4.3.0]non-5-ene (DBU) was found to be a good base for the reaction, and in nonpolar solvent toluene at 0 °C, an excellent *E*/*Z* ratio (64:1) of product **7a** was observed (Table 4, entry 9).

Encouraged by this result, we extended this synthetic methodology (using the optimized reaction conditions as those for Table 4, entry 9) to other structurally diverse terminal alkenes (see Table 5). The present one-pot procedure was found to be an efficient method to prepare (phenylsulfonyl)difluoromethylated 1,2-disubstituted alkenes **7a**−**7g** in 55−71% isolated yields and with remarkable stereoselectivity (*E*/*Z* ratio up to ≥100:1; see Table 5, entry 7).

In conclusion, an unprecedented radical (phenylsulfonyl)difluoromethylation methodology has been described by using the readily available $PhSO_2CF_2I$ as the $PhSO_2CF_2^{\bullet}$ precursor. Et_3B/air was found to be a good initiating system for the reaction, while Cu^0, $Pd(PPh_3)_4$, and $Na_2S_2O_4$ are not efficient to initiate the reaction. A one-pot procedure for the regioselective preparation of $PhSO_2CF_2$-substituted alkanes **5** has been successfully developed, by applying Et_3B/air and Bu_3SnH reagents. A remarkably regio- and stereoselective preparation of 1-substituted-2-(phenylsulfonyl)difluoromethyl alkenes **7** was achieved with the isomeric ratio *E*/*Z* up to ≥100:1. The present radical (phenysulfonyl)difluoromethylating methodology promises to find useful applications in organic synthsis, and further exploration of this interesting chemistry is underway in our laboratory.

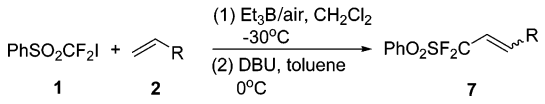
TABLE 4. Tuning the *E*/*Z* Ratio of Product 7 by Using Different Basic Reaction Conditions



entry	basic conditions	isomer ratio (*E*/*Z*)[b] **7a**
1	CH_2Cl_2, NEt_3, rt	no reaction
2	DMF, NEt_3, rt	no reaction
3	DMF, K_2CO_3, rt	6:1
4	DMF, K_2CO_3, 0 °C	7:1
5	CH_3CN, KOH, rt	4:1
6	DMF, DBU, rt	20:1
7	CH_2Cl_2, DBU, rt	27:1
8	toluene, DBU, rt	51:1
9	toluene, DBU, 0 °C	64:1

[a] Determined by ^{19}F NMR spectroscopy.

TABLE 5. Stereoselective Preparation of (Phenylsulfonyl)difluoromethylated Alkenes 7



entry	R	product	yield (%)[a]	*E*/*Z*[b]
1	1-butyl	**7a**	71	64:1
2	1-decyl	**7b**	69	70:1
3	trimethylsilyl	**7c**	69	51:1
4	$CH_3C(O)CH_2CH_2-$	**7d**	61	38:1
5	$EtOC(O)CH_2CH_2CH_2-$	**7e**	68	60:1
6	$HOCH_2-$	**7f**	58	56:1
7	*p*-$CH_3OC_6H_4OCH_2-$	**7g**	55	≥100:1

[a] Isolated yields. [b] Determined by ^{19}F NMR spectroscopy.

Experimental Section

Typical Procedure for the Radical Addition of Iododifluoromethyl Phenyl Sulfone with Alkenes. In the presence of air, into a sealed 30-mL Schlenk flask containing iododifluoromethyl phenyl sulfone (**1**) (64 mg, 0.2 mmol) and 1-hexene (**2a**) (34 mg, 0.4 mmol) in 1.2 mL of CH_2Cl_2 at −30 °C was added Et_3B (0.2 mL, 1.0 mol in hexane) via a syringe. The reaction mixture was stirred at this temperature for 0.5 h. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:30) to give product **3a** as an oily liquid, yield 75% (60 mg).

Typical Procedure for the Preparation of $PhSO_2CF_2$-Substituted Alkanes 5. In the presence of air, into a sealed 30-mL Schlenk flask containing iododifluoromethyl phenyl sulfone (**1**) (95 mg, 0.3 mmol) and 1-hexene (**2a**) (50 mg, 0.6 mmol) in 2 mL of CH_2Cl_2 at −30 °C was added Et_3B (1.0 mL, 1.0 mol in hexane) via a syringe. The reaction mixture was stirred at this temperature for 0.5 h. After the removal of volatile solvents under vacuum, to the flask were further added Bu_3SnH (114 mg, 0.39 mmol) and toluene (2.0 mL). Under N_2 atmosphere, the reaction mixture was heated for 0.5 h at 90 °C, followed by adding a saturated KF−H_2O solution (5 mL) at rt. The mixture was extracted with Et_2O (25 mL × 3), and the combined organic phase was dried over anhydrous $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:50) to give product **5a** as an oily liquid, yield 75% (62 mg).

Typical Procedure for the Preparation of $PhSO_2CF_2$-Substituted Alkanes 6. In the presence of air, into a sealed 30-mL Schlenk flask containing iododifluoromethyl phenyl sulfone (**1**) (159 mg, 0.5 mmol), vinyl ether (180 mg, 2.5 mmol), and Bu_3SnH (189 mg, 0.65 mmol) in 2.5 mL of toluene at −78 °C was added Et_3B (0.65 mL, 1.0 mol in hexane) via a syringe. The reaction mixture was stirred at this temperature for 0.5 h, followed by adding a saturated KF−H_2O solution (10 mL) at rt. The mixture was extracted with Et_2O (25 mL × 3), and the combined organic phase was dried over anhydrous $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:50) to give product **6** as an oily liquid, yield 64% (85 mg).

Typical Procedure for the Preparation of $PhSO_2CF_2$-Substituted Alkenes 7. In the presence of air, into a sealed 30-

mL Schlenk flask containing iododifluoromethyl phenyl sulfone (**1**) (318 mg, 1.0 mmol) and 1-hexene (**2a**) (168 mg, 2.0 mmol) in 6 mL of CH_2Cl_2 at −30 °C was added Et_3B (1.0 mL, 1.0 mol in hexane) via a syringe. The reaction mixture was stirred at this temperature for 0.5 h. After the removal of volatile solvents under vacuum, to the flask were further added DBU (182 mg, 1.2 mmol) and toluene (8 mL) at 0 °C. The reaction mixture was stirred at this temperature for 3.0 h, followed by removal of volatile solvents under vacuum. The crude product was further purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:50) to give product **7a** as an oily liquid, yield 71% (195 mg).

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Supporting Information Available: General experimental information and characterization data of the isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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