A Facile and Efficient Synthesis of New Fluoroalkylsulfonates and the Corresponding Tetrabutylammonium Salts

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Graphical Abstract

New fluoroalkylsulfonate and the corresponding tetra-n-butylammonium salt were synthesized from the inexpensive and commercially available fluorine-containing ester, methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (**1**), by way of nucleophilic addition of Grignard reagents.

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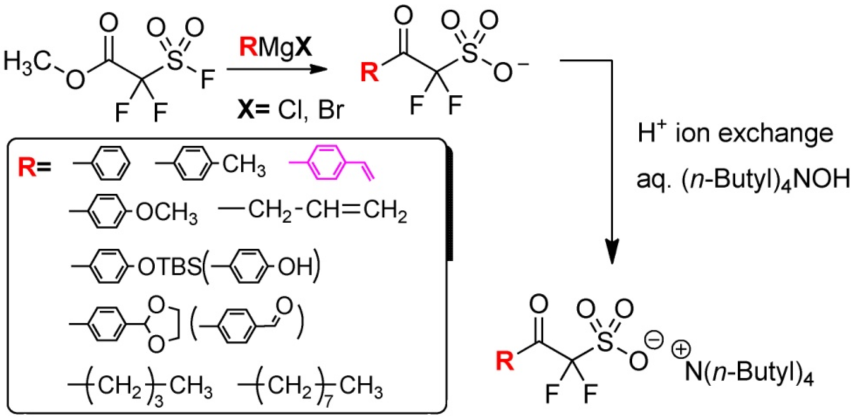
Youbing Mu[ab], *Xiaobo Wan*[ab]*



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A Facile and Efficient Synthesis of New Fluoroalkylsulfonates and the Corresponding Tetrabutylammonium Salts

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ABSTRACT

A useful synthetic methodology towards new fluoroalkylsulfonates was developed. Grignard addition to an inexpensive and commercially available fluorine-containing ester, methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (**1**) gave the mono-adduct (**2**) as the only product in high yield. The scope and limitation of this method were thoroughly investigated and it was found that it works for most Grignard reagents except electron-poor ones. Interestingly, the resulting fluoroalkylsulfonates exhibit substituent-dependent hydration behavior due to the presence of carbonyl group in these compounds. Converting the fluoroalkylsulfonate to the acid form and then neutralizing with tetra-*n*-butylammonium hydroxide gave the corresponding tetra-*n*-butylammonium salts, which shows good solubility in common organic solvents, some of which might be suitable for copolymerization with other hydrophobic monomers.

1. Introduction

Polymers with pendant sulfonate groups have been of significant interest both in academia and industry for many years. They have been used to fabricate membranes for proton exchange membrane fuel cells, water purification, and electroactive actuators,[1] or used as template for metal nanoparticles and inorganic/organic hybrid materials[2] or as additives to improve the toughness of thermoplastics.[3] More attention has been paid to those polymers with pendant fluoroalkylsulfonate groups due to their unique physical and chemical properties.[4] The traditional postpolymerization sulfonation method, however, is not applicable to incorporate the pendant fluoroalkylsulfonate groups into polymers. A commonly used approach is to directly copolymerize monomers containing pendant fluoroalkylsulfonate groups. A most famous example is Nafion, synthesized by the radical copolymerization of tetrafluoro-ethylene with monomer **I** (Figure 1), a sulfonyl fluoride-substituted perfluorovinyl ether. However, these perfluorinated vinyl ethers are costly and can only be polymerized by free radical polymerziation with a limited range of comonomers.[5] One alternative method to reduce the cost of polymer electrolytes is to use partially fluorinated hydrocarbons [4b, 6] such as styrenic monomers with a pendant fluoroalkylsulfonate group, which is readily polymerized with a wide variety of comonomers under various conditions such as anionic, cationic, coordination, and controlled radical polymerization.[5a] So far, only a few aromatic compounds with the pendant fluoroalkylsulfonate groups have been reported. [7]

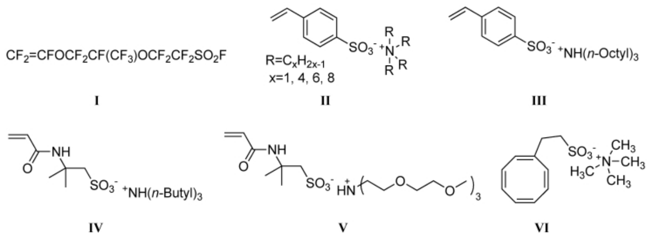


Figure 1. Perfluorinated vinyl ethers and various types of substituted ammonium sulfonate monomer

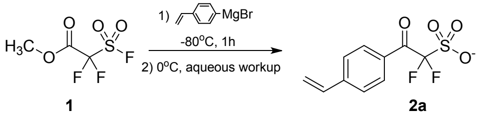
On the other hand, most commercially available sulfonate monomers are in the acid or alkali salt form which endows them with the ability to copolymerize with other polar monomers. However, their poor solubility in organic solvents limit their copolymerization with a wider range of hydrophobic monomers.[8] To overcome these drawbacks, these monomers could be either converted to the corresponding sulfonate esters, which requires the use of water sensitive sulfonyl chlorides or photosensitive silver salts,[9] or to exchange the counterion to a more hydrophobic one.[10] The later is no doubt the more economic route. Actually, various types of tetra-*n*-butylammonium salts are used as monomers, such as monomer **II**,[10g] **III**, [10f] **IV**, [11] **V**[10e, 10h] and **VI**[12] (Figure 1), which have been polymerized by traditional/living radical polymerization methods and successfully applied for advanced materials.

We now wish to report an effective method for the synthesis of a series of fluoroalkylsulfonates (**2**) via Grignard reaction with an inexpensive and commercially available fluorine-containing ester, methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (**1**), including the polymerizable monomer **2a**.The scope and limitation of the this method is thoroughly screened, which shows a wide-range viability. Furthermore, a hydration equilibrium on the carbonyl group in these magnesium fluoroalkylsulfonates in aqueous solution is observed, which is strongly dependent on the substituent next to it. These fluoroalkylsulfonates could be converted quantitatively to the corresponding tetra-*n*-butyl-ammonium salts, some of which should be suitable for polymerization with hydrophobic monomers.

2. Results and discussion

Esters with fluorinated α-carbon have been demonstrated to be useful substrates to construct the corresponding ketones by low temperature reaction (-80 °C) with Grignard reagents.[13] However, except for trifluoroacetate, other esters with fluorinated α-carbon still suffer from bis-addition and reduction side products.[13] For example, addition of PhMgBr to n-$C_3F_7CO_2Et$ produces 1,1-diphenyl-perfluorobutan-1-ol almost exclusively.[13a] Reduction product sometimes dominates when THF is used as the solvent.[13b] We investigated in detail the addition reaction of **1** with (4-vinylphenyl)magnesium bromide under various conditions. Surprisingly, a 1,1-difluoro-2-oxo-ethanesulfonate salt **2a**, was formed exclusively in a yield higher than 79% under all the experimental conditions (Table 1). It is found that No bisadduct or reductive products were found even when excess Grignard reagent was used (entry 3, Table 1). The results also show that unlike the reported case,[13b] different reaction medias have no obvious influence on the yield.

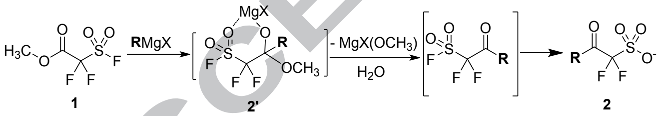
Table 1. Reaction of (4-vinylphenyl)magnesium bromide with methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (**1**)



Entry	$n_G{}^a/n_1$	Solvent^b	Isolated yield (%)
1	1.1:1	THF(THF)	82
2	1.5:1	THF(THF)	86
3	2:1	THF(THF)	86
4	1.1:1	Tol(THF)	81
5	1.5:1	Tol(THF)	84
6	1.1:1	Et_2O(THF)	79

[a] G was used for the abbreviation of Grignard reagent.

[b] In the parenthesis was shown the solvent for the Grignard reagent.

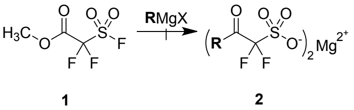


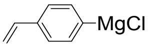
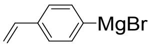
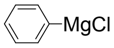
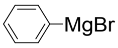
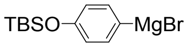
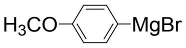
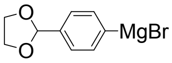
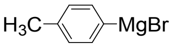
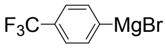
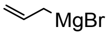
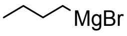
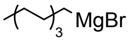
Scheme1. The reaction mechanism of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (**1**) and Grignard reagents

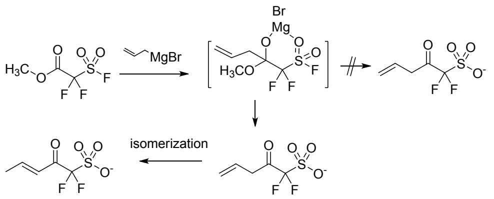
All these evidences indicate that the FSO_2CF_2- group plays an important role in stabilize the tetrahedron addition intermediate, as the reaction mechanism proposed in Scheme 1. We assume that the Grignard reagents RMgX would initiate this transformation by the nucleophilic attack at the ester carbonyl carbon atom of **1** to furnish the tetrahedral intermediate. Besides the electron-withdrawing effect of the difluoromethine group, [13] the tetrahedral intermediate is also stabilized by the chelation of the magnesium by both the oxygen atom originally belong to the carbonyl group and the oxygen atom on the sulfonate group, which prohibits the collapse of intermediates (**2′**) thus avoids the reformation of the carbonyl group and further addition that leads to bisadduct. Thus, upon aqueous workup, it could smoothly yield ketone by releasing $MgX(OCH_3)$ and the hydrolysis of the sulfonyl fluoride group leads to the final fluoroalkylsulfonate **(2)**. The electron-withdrawing sulfonyl fluoride group may also contribute to the stabilizing effect.

We have shown that **2a** and **2b** could be synthesized in a previous patent,[7b] and now to validate the effectiveness of above method, we extended this methodology to other Grignard reagents to test the scope and limitations of this reaction, and the results are summarized in Table 2. Briefly, as shown in Table 2 (entry 1 to 4), the bromide Grignard reagents gave higher yield than chloride Grignard reagents. Furthermore, the electronic nature of the substituents on the *para* position of phenyl rings has a profound effect on the yield. The introduction of electron donating group slightly decreased the yield. With TBSO-, the yield was 75% (**2c**) while for CH_3-, the yield was 67% (**2f**). The introduction of strong electron-withdrawing group at *para* position inhibited the reaction (**2g**). Vinylmagnesium bromide was also tested (**2h**), however, a large amount of unidentified mixture was obtained, which might be due to the instability of the resulting easily-accessible and highly reactive α,β-unsaturated ketone which is vulnerable towards nucleophilic attack. Switching to allylmagnesium bromide led to a pure product which is identified to be the isomerized product (**2i**). The isomerization is driven by the formation of a more stable α,β-unsaturated ketone, and the terminal methyl group endows steric hinderance to the alkene which protect it from decomposition (Scheme 2). For the saturated alkyl Grignard reagents, **2j** or **2k** was isolated as the major product in >60% yield. Compound **2** series have good solubility in water and the pH value of the solution is neutral, indicating that they are salts. In order to confirm the counter cation, the Energy Dispersive Spectrometry (EDS) technique was employed and the results showed that the cation is magnesium ion.

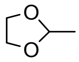
Table 2. The reaction of methyl 2,2-difluoro-2-(fluorosulfonyl) acetate (**1**) with different Grignard reagents



Entry	RMgX	Product	Isolatedyield (%)
1		**2a**	70
2		**2a**	86
3		**2b**	68
4		**2b**	90
5		**2c**	75
6		**2d**	73
7		**2e**	71
8		**2f**	67
9		**2g**	-
10		**2h**	-
11		**2i**	77
12		**2j**	69
13		**2k**	65



Scheme 2. Isomerization process of **2i**

Like *p*-nitrobenzadehyde and 3-fluoroacetophene, the carbonyl group on compound **2** could be hydrated in the presence of water due to the electron withdrawing ability of the adjacent R_F.[14] The hydrated product coexists with the unhydrated one, which could be verified by the ^{1}H NMR spectra. Typical ^{1}H NMR spectra in different deuterated solvents are shown in Figure 2, using **2a** as the example. In D_2O, two different sets of peaks were observed. The peaks a, b and c are assigned to the three protons on the double bond of **2a** in the D_2O (Figure 2A) and DMSO-d_6 (Figure 2B). The peaks at 6.7 ppm (c′), 5.8 ppm (b′) and 5.3 ppm (a′) are assigned to the three protons on the double bond of the hydrate in the D_2O, while these peaks were not found in the DMSO-d_6. This difference indicates that there exists a balance between **2a** and its hydrate. Hydration was further confirmed by high resolution mass spectrum, where the molecular ion peak at 293.0273 is assigned to the methanol adduct (Figure 3). Other products (**2b-f** and **2i-k)** were also tested and the equilibrium constant ($K_1[H_2O]$) was calculated by the integral of hydrate in the ^{1}H NMR spectrum**.** The results are shown in Table 3. For **2b-f**, the equilibrium constant was found to be dependent on the electronic nature of the *para* substituents on the phenyl rings. With the substituent's electron-donating capacity increasing in the order of H-, CH_2=CH-, CH_3-, CH_3O-,  and TBSO-, the equilibrium constant decreased from 0.51 to zero. The equilibrium constant of the saturated alkyl substituent was 0.16 and did not change with the increase of chain length. Interestingly, in the presence of vinylic substituent, no hydrate could be found and the equilibrium constant was zero.

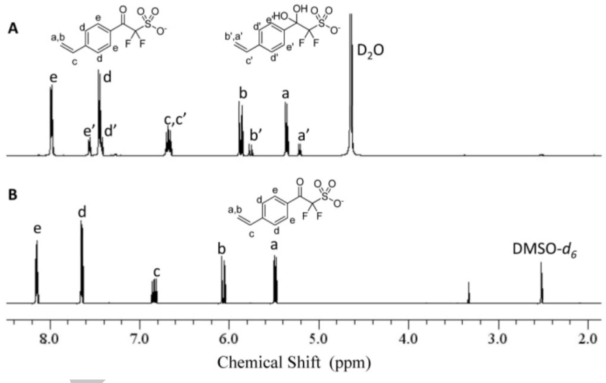


Figure 2. ^{1}H NMR spectra of **2a** in D_2O (A) and DMSO-d_6 (B)

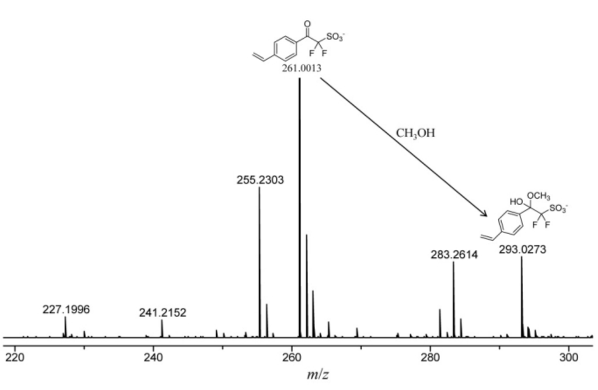
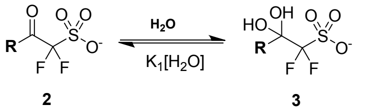


Figure 3. The mass spectrum of **2a** in methanol

Table 3. The equilibrium constant of **2** and its hydrate



2 3

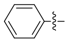
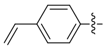
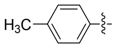
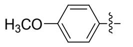
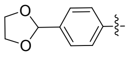
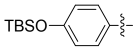
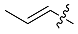
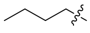
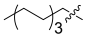
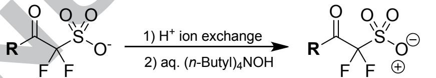
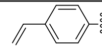
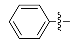
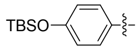
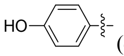
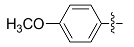
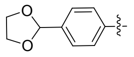
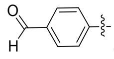
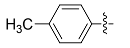
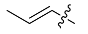
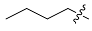
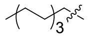
Entry	R	$K_1[H_2O]$
1		0.51
2		0.30
3		0.12
4		0.08
5		0.06
6		0.00
7		0.00
8		0.16
9		0.16

Table 4. The scheme and yield of neutralization with tetra-*n*-butylammonium hydroxide



2a-f, 2i-k

4

Entry	2a-f, 2i-k	4	Isolated yield (%)
	R	R_1	
1		**R_1=R (4a)**	99
2		**R_1=R (4b)**	98
3		 (**4c**^{1})	98
4		**R_1=R(4d)**	98
5		 (**4e**^{1})	97
6		**R_1=R(4f)**	98
7		**R_1=R(4i)**	99
8		**R_1=R(4j)**	98
9		**R_1=R(4k)**	99

Although compound **2** series show excellent solubility in highly polar solvents such as water, dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF), they exhibit very low solubility in acetone, tetrahydrofuran (THF) and methanol. This limited solubility would restrict its application. Thus, in order to improve the solubility, the fluoroalkylsulfonates were converted to the acid form and subsequently neutralized with tetra-n-butylammonium hydroxide aqueous solution. To our delight, white precipitates were easily obtained from the aqueous solution and separated by filtration in almost quantitative yield (Table 4). A typical ^{1}H NMR spectrum confirmed that the solid was the pure quaternary ammonium sulfonate product (**4a**), using **2a** as the example (Figure 4). The peaks a, b, c, d and e are assigned to the protons on the styryl group of **4a**, and the peaks f, g, h and i are assigned to the protons on the *n*-butyl group of **4a**. The integrals of this two group protons match well, indicating that pure ammonium fluoroalkylsulfonates have been obtained. It should be noted that, due to the instability of TBS group (**2c**) and acetal group (**2e**) under the acid conditions, the **2c** and **2e** should be deprotected to give the phenol and formaldehyde before neutralization. Just like the lipophilicity of other reported monomers with tetra-n-butylammonium cation, compound **4** series are readily soluble in a wide range of solvents including chloroform, benzene, acetone, anisole, tetrahydrofuran, *N*,*N*-dimethylformamide, *N*-methyl-2-pyrrolidone and methanol at room temperature at a high concentration (>500 mg/mL), which makes **4a** and **4i** copolymerizable with a wider range of hydrophobic monomers.

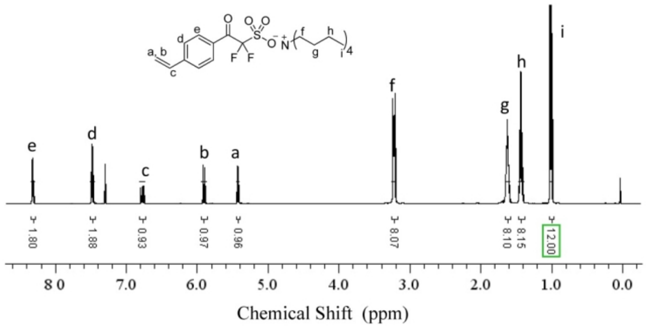


Figure 4. ^{1}H NMR spectrum of **4a** in CDCl$_3$

3. Conclusion

As described above, we have investigated the addition reaction of Grignard reagents to an inexpensive and commercially available substrate **1** which led to the formation of a series of fluoroalkylsulfonate **2** in high yield, including monomer **2a** for suitable for polystyrenic super acid. The neighboring sulfonyl group may play a vital role in controlling the reaction, in which its participation in the chelation of magnesium salt prohibits the collapse of the tetrahedron intermediate, avoiding the bisadduct and reduction side product that is normally observed in the Grignard addition to esters with fluorinated α-carbon. Most electron-rich Grignard regents give good yield, while electron-poor Grignard regent does not work. We also observed that the carbonyl moiety on the product exists in an equilibrium with its hydrated form in aqueous solutions, the extent of which is strongly dependent on the electron-donating character of the substituent next to the carbonyl group. Subsequently, converting the adducts to the acid form and then neutralizing them with tetra-*n*-butylammonium hydroxide in aqueous solution gave the corresponding tetra-*n*-butylammonium salts **4** quantitatively**,** which shows good solubility in common organic solvents. Currently, an effort is underway to study the polymerization of the corresponding monomers and the applications for advanced materials. These results will be reported in due course.

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Highlights

- New fluoroalkylsulfonates were synthesized by Grignard addition reaction.
- The sulfonyl group helps to stabilize the tetrahedron intermediate to avoid side reactions.
- The hydration behavior of fluoroalkylsulfonate was studied.
- Tetra-*n*-butylammonium fluoroalkylsulfonates were easily prepared quantitatively..