

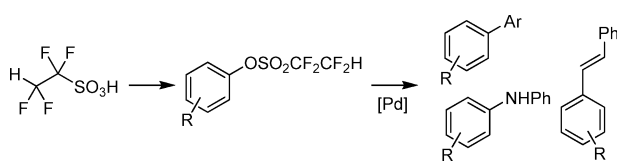
Preparation and Synthetic Applications of Aryl Tetraflates (ArOSO₂CF₂CF₂H)

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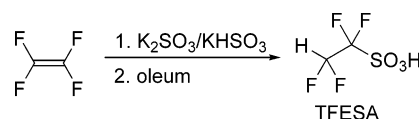
Received July 30, 2007



We have recently developed an improved synthetic route to 1,1,2,2-tetrafluoroethanesulfonic acid (HCF₂CF₂SO₃H, TFESA) and explored the applications of this newly available superacid in catalysis. Low volatility, ease of handling, and a convenient ¹H NMR handle make this acid an attractive alternative to triflic acid. TFESA can also be converted to several of its derivatives: anhydride, sulfonyl chloride, and sulfonyl fluoride, which provide a good entry point for the synthesis of aryl sulfonates. We prepared several aryl esters of 1,1,2,2-tetrafluoroethanesulfonic acid (aryl tetraflates) and showed that they can be used in a number of palladium-catalyzed coupling reactions (Suzuki, Heck, and Buchwald–Hartwig couplings). While the reactivity of tetraflates lies between that of triflates and chlorides, tetraflates appear to be more thermally stable. Additionally, the presence of a hydrogen atom in the tetraflate group facilitates monitoring of reactions and characterization of derivatives.

Triflate (CF₃SO₂[−]) and nonaflate (C₄F₉SO₂[−]) derivatives are widely used in organic chemistry as synthetic intermediates.^{1–4} Aryl triflates and nonaflates can be conveniently prepared from phenols and sulfonic acid anhydrides or fluorides. Perfluoroalkanesulfonyl esters of 4-nitrophenol can also be used as sulfonyl transfer agents for the synthesis of aryl triflates and nonaflates.^{5,6} The presence of a fluorinated sulfonate ester activates the carbon–oxygen bond of the phenol, so that aryl triflates and nonaflates become substrates for a number of

SCHEME 1. Preparation of TFESA



palladium-catalyzed reactions such as Suzuki coupling,⁷ Heck reaction,^{8,9} and Buchwald–Hartwig aminations.¹⁰ The reactivity of these derivatives in coupling reactions falls somewhere between that of aryl chlorides and aryl bromides.¹

Derivatives of longer chain perfluoroalkanesulfonic acids show similar reactivity and were explored for use in fluororous technologies.^{11,12}

We have recently reported the synthesis of a series of fluorinated sulfonate salts and sulfonic acids.^{13–15} Addition of sulfites to a variety of fluoroolefins and perfluorovinyl ethers provides a convenient and practical preparation of the corresponding salts, which can be further converted to sulfonic acids. For example, potassium 1,1,2,2-tetrafluoroethanesulfonate (or tetraflate) was prepared from tetrafluoroethylene in a buffered aqueous solution of potassium sulfite and bisulfite and then converted to 1,1,2,2-tetrafluoroethanesulfonic acid (TFESA) in 90% overall yield by distillation from oleum (Scheme 1).¹⁵

TFESA is a convenient starting point for the preparation of a number of acid derivatives. Here, we report the preparation of 1,1,2,2-tetrafluoroethanesulfonyl chloride (**1**), fluoride (**2**), anhydride (**3**), and aryl esters of TFESA (aryl tetraflates). We also examined the utility of aryl tetraflates in Suzuki, Heck, and Buchwald–Hartwig reactions.

1,1,2,2-Tetrafluoroethanesulfonic acid anhydride (TFESAA) was prepared in moderate yields by distillation from P₄O₁₀, following the procedure reported for triflic anhydride (Scheme 1).¹⁶ TFESAA is a colorless liquid that starts to decompose when heated above 105 °C.¹⁷ It can be distilled at 80–100 °C under reduced pressure.

Synthesis of the chloride was disclosed in a Hoechst patent¹⁸ and the same method was used in this work to obtain sulfonyl chloride **1** from TFESA in excellent yields (Scheme 2). The product is a colorless liquid with a boiling point of 104 °C at 1 atm. Treatment of **1** with CsF in sulfolane solvent, followed by distillation afforded sulfonyl fluoride **2** in 83% yield. Fluoride

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SCHEME 2. Preparation of Tetraflate Derivatives

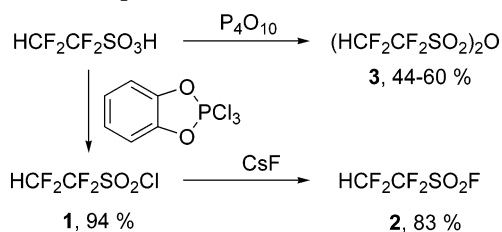


TABLE 1. Preparation of Tetraflates

X	R (product)	base	time, h	yield, %
Cl	4- <i>t</i> -Bu, 5	Et ₃ N	17	94
Cl	4-NO ₂ , 6	Et ₃ N	4	92
Cl	4-OMe, 4	Et ₃ N	2	94
F	2,6-(Me) ₂ , 7	DBU	3.5	93
F	4- <i>t</i> -Bu, 5	DBU	1	99
OSO ₂ CF ₂ CF ₂ H	4- <i>t</i> -Bu, 5	Pyridine	4	84

2 can also be prepared by treatment with KF/KHF₂ in acetonitrile, as reported by Hoechst researchers.¹⁸

We used HCF₂CF₂SO₂Cl, HCF₂CF₂SO₂F, and (HCF₂CF₂SO₂)₂O to prepare aryl tetraflates from phenols using methods typically used for the preparation of aryl triflates (Table 1).^{1,2} Sulfonyl chloride **1** worked well with both electron-poor and electron-rich phenols (*p*-nitro and *p*-methoxy, respectively), but gave very low yields with sterically crowded 2,6-dimethylphenol. The latter was successfully converted to its tetraflate with HCF₂CF₂SO₂F. All three derivatives can be used with 4-*tert*-butylphenol to give 4-*tert*-butylphenyltetraflate in good to excellent yields.

The presence of hydrogen in the 1,1,2,2-tetrafluoroethane sulfonyl group allows the use of ¹H NMR for characterization of tetraflate derivatives. A fragment of the ¹H NMR spectrum of 4-methoxyphenyl tetraflate is shown in Figure 1. In addition to peaks in the aromatic region, which belong to the substituted phenyl group, there is a triplet of triplets centered at 6.22 ppm. This signal was assigned to the proton of the tetraflate group and it is split by two sets of CF₂ groups. In contrast to triflate and other perfluoroalkylsulfonate groups, we found that the presence of this ¹H NMR feature greatly facilitates not only characterization of tetraflate derivatives but also monitoring of their reactions.

We compared thermal properties of 4-nitrophenylfluorosulfonates derived from trifluoromethanesulfonic, nonafluorobutanesulfonic, and 1,1,2,2-tetrafluoroethanesulfonic acids by thermogravimetric analysis (Table 2).²⁸ We found that 10% and 50% weight losses for tetraflate occur at considerably higher temperatures compared to nonaflate and triflate esters. For example, 4-nitrophenyl triflate loses 10% of its weight at 105 °C, 4-nitrophenyl nonaflate loses 10% at 125 °C, but tetraflate only reaches the same weight loss at 150 °C. A similar trend is seen for 50% weight loss. To better understand thermal properties of these materials, we also measured their melting points. Surprisingly, tetraflate has the lowest melting point (Table 2). This unexpected property of aryl tetraflates, which might be due to lower volatility of these derivatives, opens up the possibility of using higher temperatures for their transformations.

The proton of the tetraflate group appears to be stable in the presence of strong bases.^{19,20} 4-*tert*-Butylphenyl tetraflate was treated with *n*-BuLi in Et₂O for 30 min at -78 °C followed by methanol-*d*₄ quench. Starting tetraflate was recovered in 40% yield. By ¹H and ¹⁹F NMR, the balance consisted of 4-*tert*-butylphenol and lithium 1,1,2,2-tetrafluoroethanesulfonate. No deuterium incorporation into the HCF₂CF₂- group or traces of other fluorine-containing byproducts was observed, implying that sulfonate ester hydrolysis happens before deprotonation.

Suzuki coupling of aryl sulfonates with aryl boronic acids is used widely for the formation of carbon-carbon bonds.⁷ Triflates,²¹ nonaflates,²² and perfluoroalkylsulfonates²³ can all be used successfully for this transformation. We found that aryl tetraflates behave similarly to triflates in these reactions (Table 3). Under conditions reported by Fu and co-workers (Pd(OAc)₂/PCy₃/CsF in THF at 55 °C),²¹ 4'-substituted 2-methylbiphenyls were obtained in good yields (86–94%). However, sterically hindered 2,6-dimethylphenyl tetraflate gave only traces of the product.

Fluorinated aryl sulfonates such as triflates, nonaflates, or perfluoroalkylsulfonates have also been extensively used in palladium-catalyzed aminations.^{11,24–26} In our hands, amination of aryl tetraflates with aniline afforded diarylamines in good yields (57–86%, Table 4). The yield was highest for 4-*tert*-butylphenyl tetraflate, while 4-nitro- and 4-methoxyphenyl tetraflates gave lower yields of the desired products. We also found that the Xanthos ligand had to be used for the coupling of 4-nitrophenyltetraflate.

Aryl tetraflates can also be used in Heck coupling (Table 5). We employed conditions reported by Norrby and co-workers for reactions of aryl triflates (5 mol % Pd₂(dba)₃, 10 mol % 1,3-bis(diphenylphosphino)propane or dppp, Et₃N, DMF, 80 °C)²⁷ and compared yields and selectivities of triflate couplings with those for aryl tetraflates. With 4-nitrophenyl tetraflate, Xanthphos and DBU were used instead of dppp and Et₃N, respectively. In all cases we obtained good to excellent yields of substituted styrenes. 4-Nitro- and 4-*tert*-butylphenyl tetraflates gave mostly β-substituted styrenes, while 4-methoxyphenyl tetraflate afforded a 1:1 mixture of α and β isomers. Norrby and co-workers reported that reaction between phenyl triflate and several 4-substituted styrenes also gave a mixture of isomers: 1:0.81 and 1:0.89 for 4-methoxy and 4-methyl, respectively, at low conversions.²⁷ Interestingly, 4-trifluoromethylstyrene gave predominantly the 1,2-isomer (1:0.23 at low

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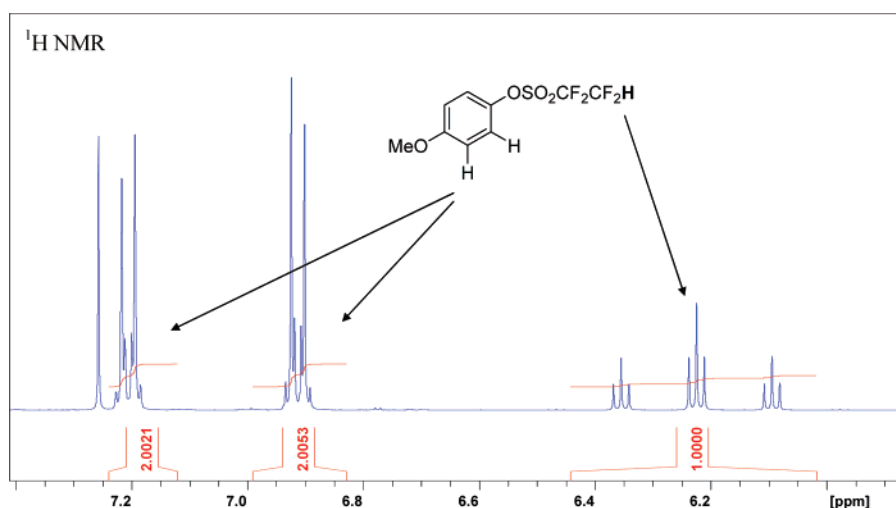


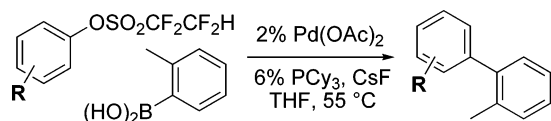
FIGURE 1. Part of the ^1H NMR spectrum of 4-methoxyphenyltetraflate in CDCl_3 .

TABLE 2. Thermal Properties of 4-Nitrophenylsulfonates, $\text{ArOSO}_2\text{R}_F^a$

R_F	$T_{10\%}$	$T_{50\%}$	mp, $^\circ\text{C}$
CF_3	105	128	52–53 ⁵
HCF_2CF_2	150	190	24
$\text{CF}_3\text{CF}_2\text{CF}_2\text{CF}_2$	125	158	70 ⁵

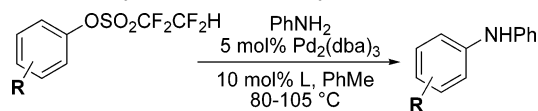
^a Temperatures of 10% and 50% weight loss, by TGA.

TABLE 3. Suzuki Coupling with Aryl Tetraflates



entry	R	time, h	yield, %
1	4- <i>t</i> -Bu	17	86
2	4- NO_2	17	94
3	4-OMe	16	90
4	2,6-(Me) ₂	40	4

TABLE 4. Catalytic Amination of Aryl Tetraflates^a



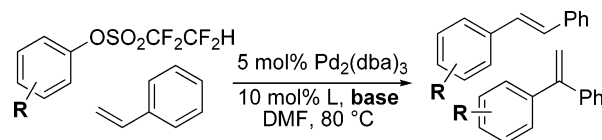
entry	R	L	temp, $^\circ\text{C}$	time, h	yield, %
1	4- <i>t</i> -Bu	BPCy ₂	80	18	86
2	4- NO_2	XantPhos	105	40	57
3	4-OMe	BPCy ₂	80	16	60

^a See the Supporting Information for ligand structures.

conversion). It appears that the presence of electron-withdrawing groups favors the formation of the 1,2-regioisomer.

In summary, it has been demonstrated that aryl esters of 1,1,2,2-tetrafluoroethanesulfonic acid (aryl tetraflates) can be used in a number of palladium-catalyzed coupling reactions. While the reactivity of tetraflates is similar to that of triflates and chlorides, tetraflates appear to be more thermally stable. Additionally, the presence of the hydrogen atom in the tetraflate group facilitates monitoring of reactions and characterization of derivatives.

TABLE 5. Heck Coupling with Aryl Tetraflates



entry	R	ligand L	base	time, h	yield, %
1	4- <i>t</i> -Bu	dppp	Et_3N	21	68 (6:1) ^a
2	4- NO_2	XantPhos	DBU	42	71 (50:1) ^a
3	4-OMe	dppp	Et_3N	21	89 (1:1) ^a

^a Ratio of 1,2- to 1,1-isomers; see the Supporting Information for ligand structures.

Experimental Procedures

Preparation of 1,1,2,2-Tetrafluoroethanesulfonyl Chloride (1).¹⁸ This procedure was carried out in a drybox (TFESA is hygroscopic). To an oven-dried 250-mL round-bottomed flask charged with 57.25 g of catechylphosphorous trichloride (0.233 mol, 1.2 equiv) was added 35.4 g of 1,1,2,2-tetrafluoroethanesulfonic acid (0.194 mol, 1.0 equiv) slowly to keep the gas evolution under control. After 1 h, the gas evolution had ceased but undissolved catechylphosphorous trichloride remained. The reaction flask was removed from the drybox, and a distillation head was attached under nitrogen atmosphere. The reaction mixture was heated in an 80 $^\circ\text{C}$ oil bath for 2 h. A clear, light-brown solution was obtained after 30 min of heating. The oil bath temperature was raised to 140 $^\circ\text{C}$ to begin the distillation and slowly increased to 190 $^\circ\text{C}$. One fraction, with a boiling point range of 84–88 $^\circ\text{C}$ (lit.¹⁸ 90 $^\circ\text{C}$), yielded 36.73 g (94%) of a clear colorless liquid. Identity was confirmed by ^1H and ^{19}F NMR.¹⁸ ^1H NMR (400 MHz, CDCl_3) δ 6.27 (1H, tt, $^2J_{\text{HF}} = 51.9$ Hz). ^{19}F NMR (400 MHz, CDCl_3) δ -111.9 (2F, m), -133.6 (2F, dt, $^2J_{\text{HF}} = 51.9$ Hz).

Preparation of 1,1,2,2-Tetrafluoroethanesulfonyl Fluoride (2).¹⁸ In a drybox, an oven-dried two-necked 100-mL round-bottomed flask was charged with 15.0 g of 1,1,2,2-tetrafluoroethanesulfonyl chloride (74.8 mmol) and 17.9 g of dry cesium fluoride (112.2 mmol). The flask was brought out of the drybox and a short-path distillation head was attached under nitrogen atmosphere. To this was added 25 mL of dry sulfolane, warmed in a 55 $^\circ\text{C}$ oil bath, using a hot syringe to prevent the sulfolane from solidifying. The reaction mixture was stirred at room temperature for 88 h until reaction was complete as judged by ^{19}F NMR monitoring. The receiving flask was cooled with a dry ice/acetone bath and product was transferred out of the reaction mixture under

reduced pressure and with vigorous stirring. 1,1,2,2-Tetrafluoroethanesulfonyl fluoride (11.4 g, 82.6%) was collected as a clear colorless liquid. Identity was confirmed by ^1H and ^{19}F NMR. ^{18}H NMR (400 MHz, CDCl_3) δ 6.21 (1H, tt, $^2J_{\text{HF}} = 51.75$ Hz). ^{19}F NMR (400 MHz, CDCl_3) δ 44.4 (1F, m), -114.9 (2F, m), -135.1 (2F, dq, $^2J_{\text{HF}} = 51.9$ Hz).

Preparation of 1,1,2,2-Tetrafluoroethanesulfonic Acid Anhydride (3). An oven-dried 500-mL round-bottomed flask was charged with 40 g of sand, 82.0 g (57.7 mmol) of phosphorus pentoxide, and a magnetic stir bar. The flask was swirled by hand, and was warm to the touch. A short-path distillation column was attached and the reaction flask was twice evacuated and filled with nitrogen atmosphere. 1,1,2,2-Tetrafluoroethanesulfonic acid (41.09 g, 23.0 mmol) was added and the flask was evacuated and filled with nitrogen once more. The reaction mixture was warmed in a 65°C oil bath and began to turn dark brown. The reaction mixture was kept at 65°C for 3 h, followed by 16 h at room temperature. Distillation was carried out at 75°C under vacuum (60 mT, vapor pressure of **3** is 15 Torr at 72°C) giving 20.44 g of 1,1,2,2-tetrafluoroethanesulfonic acid anhydride (44%) as a clear colorless liquid. The product was stored in a drybox. ^1H NMR (400 MHz, CDCl_3) δ 6.24 (1H, tt, $^2J_{\text{HF}} = 51.7$ Hz). ^{19}F NMR (400 MHz, CDCl_3) δ -112.7 (4F, m), -134.3 (4F, dq, $^2J_{\text{HF}} = 51.7$ Hz). Anal. Calcd for $\text{C}_4\text{H}_2\text{F}_8\text{O}_5\text{S}_2$: C, 13.88; H, 0.58; F, 43.91. Found: C, 13.85; H, 0.53; F, 44.16.

Preparation of 4-tert-Butylphenyl-1,1,2,2-tetrafluoroethanesulfonate (5). An oven-dried three-necked 250-mL round-bottomed flask was charged with 1.8 g (12.0 mmol, 1.0 equiv) of 4-tert-butylphenol, 20 mL of dichloromethane, and 2.2 mL (15.6 mmol, 1.3 equiv) of triethylamine under nitrogen atmosphere. The mixture was cooled with a dry ice/acetone bath to -40°C and a solution

of 3.01 g of 1,1,2,2-tetrafluoroethanesulfonyl chloride (15 mmol, 1.25 equiv) in 5 mL of dichloromethane was added portion wise. The reaction mixture was allowed to stir cold and then was left to gradually warm to room temperature overnight. Diethyl ether (100 mL) was added and reaction mixture was transferred to a separatory funnel. The organic layer was washed twice with water and once with brine, dried over MgSO_4 , and concentrated. The crude product was passed through a 4 in. plug of silica gel, using 400 mL of ether. Ether was removed under reduced pressure to yield 3.56 g (94.4%) of 4-tert-butylphenyl-1,1,2,2-tetrafluoroethane sulfonate as a pale yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 1.32 (9H, s), 6.23 (1H, tt, $^2J_{\text{HF}} = 52.3$ Hz), 7.19 (2H, app d), 7.43 (2H, app d). ^{19}F NMR (400 MHz, CDCl_3) δ -117.15 (2F, m), -135.3 (2F, dt, $^2J_{\text{HF}} = 52.3$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ 31.05, 34.67, 108.02 ($^1J_{\text{CF}} = 256$ Hz, $^2J_{\text{CF}} = 29.5$ Hz), 114.99 ($^1J_{\text{CF}} = 294$ Hz, $^2J_{\text{CF}} = 28.4$ Hz), 120.94, 127.18, 147.72, 151.83. IR (KBr pellet) 2968 (m), 1504 (m), 1416 (s), 1209 (s), 1190 (m), 1165 (s), 1137 (s), 888 (s). Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{F}_4\text{O}_3\text{S}$: C 45.86; H 4.49; F, 24.18. Found: C, 46.04; H, 4.69; F, 24.14.

Acknowledgment. The authors would like to thank the DuPont NMR group for technical assistance and Drs. V. Petrov, M. Tisack, A. Sievert, and L. Sprague for many helpful discussions.

Supporting Information Available: General information for synthetic procedures and compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO701630A