Note

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Ethenesulfonyl Fluoride (ESF): An On-Water Procedure for the Kilogram-Scale Preparation.

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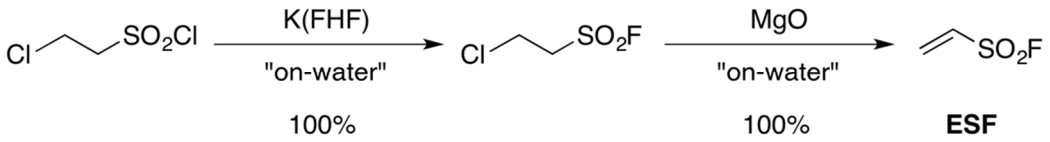


Abstract: A two-step, on-water procedure for the synthesis of ethenesulfonyl fluoride (ESF) is described. 2-Chloroethanesulfonyl fluoride is made via a neat reaction with an aqueous, near saturated potassium bifluoride solution from readily available 2-chloroethanesulfonyl chloride. The subsequent dehydrochlorination of 2-chloroethanesulfonyl fluoride proceeds neatly with magnesium oxide as the base in an aqueous suspension to give ESF. This recipe enables the preparation of ESF in 98% yield on kilogram scale.

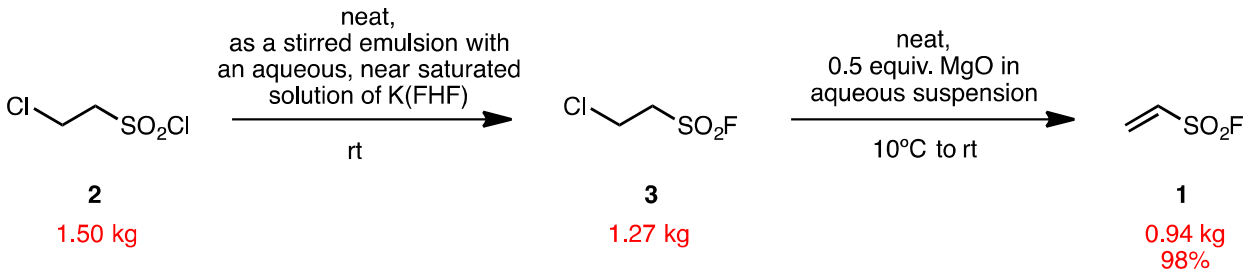
Ethenesulfonyl fluoride (ESF, **1**) consists of a vinyl moiety directly linked to a sulfonyl fluoride group (CH_2=CH–SO_2F). First reported in 1953,[1] this compound has been successfully applied to several productive fields, including: dyestuffs,[2] functional materials (ion exchange membrane,[3] photoresist material,[4] etc.), lubricating oil additives,[5] and medicinal chemistry.[6] The most noteworthy feature is that ESF ranks tops in the reactivity hierarchy of known Michael acceptors, from which most of the aforementioned applications stemmed.[7] The extraordinary Michael reactivity of ESF was demonstrated in depth by John Hyatt and co-

workers in a masterful 1979 full paper,[8] where nearly 100 examples at 1/20 mol or larger scale are presented. In our ongoing pursuit of the best small and connective modules for click chemistry,[9] ESF appears to be the perfect one. At present, the uses of ESF in a wider range of applications are limited by its high price.

Earlier routes to ESF include: (1) aqueous potassium fluoride mediated chloride-fluoride exchange from ethenesulfonyl chloride;[1] (2) chloride-fluoride exchange from 2-chloroethanesulfonyl chloride followed by a base-mediated dehydrochlorination.[10] In 1979 Hyatt et al. summarized previous syntheses and reported a two-step synthesis on a 1.7 mole scale (54% overall yield).[8] From our experience with "on-water" reactivity, we saw opportunities for further improvements. In 2012, we discovered that interfacial-treatment with saturated aqueous K(FHF) solution (pH around 3.0) was remarkably effective for the synthesis of sulfonyl fluorides from the corresponding sulfonyl chlorides.[7a] Given here are complete details of our bifluoride improved process for $RSO_2Cl \rightarrow RSO_2F$, as applied in the conversion of 2-chloroethanesulfonyl chloride (**2**) to ESF on a kilogram scale.

As shown in Scheme 1, the readily available **2** is converted to ESF in two simple steps: First, 2-chloroethanesulfonyl fluoride (**3**) is made via the sulfonyl chloride-fluoride exchange using saturated K(FHF) solution; Second, MgO mediated elimination (dehydrochlorination) of **3** in aqueous medium affords **1**.

Scheme 1. Kilogram-scale preparation of ethenesulfonyl fluoride



A 10-L Nalgene® polypropylene carboy[11] was equipped with a Teflon®-coated octagonal stir bar (14 mm × 74 mm). This reaction vessel was charged with water (4400 mL), to which potassium bifluoride [K(FHF), 1.70 kg, 21.8 mol] was added in one portion. With a magnetic stirring (600 rpm), K(FHF) started to dissolve into water, and a rapid endotherm was observed (internal temperature reached ~ 8 °C). A near saturated K(FHF) solution formed after 1 h,[12] when the solution approached room temperature (~ 22 °C). At this point, **2** (960 mL, 1.50 kg, 95% purity, 8.73 mol) was added in one portion to the K(FHF) solution. The biphasic mixture was stirred vigorously (480 rpm) to form an emulsion and with continued stirring the emulsion was maintained for 2 h at room temperature, or rather, autogenous temperature,[13] when ^{1}H NMR or GC-MS indicated the completion of the reaction. The stationary mixture separates into two phases. The upper phase is an aqueous solution of salts,[14] and the lower phase is virtually pure 2-chloroethanesulfonyl fluoride. With the aid of a funnel, the biphasic mixture was poured into a 6-L separatory funnel. The lower phase (ca. 750 mL) was drained into a 1000-mL glass Erlenmeyer flask, dried over anhydrous $MgSO_4$ (10 g), and filtered, giving **3** (1.10 kg, 7.51 mol). Three 1000-mL portions of methylene chloride were used to wash the reaction vessel and the $MgSO_4$ used to dry neat **3**, and to extract the upper aqueous phase. The combined organic phase was washed by 2 L brine,

dried over 100 g anhydrous $MgSO_4$, and filtered through a 600-mL sintered glass Buchner funnel. The filtrate was concentrated by rotary evaporation (18 °C, 0.05 bar) to afford additional 0.17 kg **3**. In total, **3** (1.27 kg, 8.67 mol, 99.3%) was obtained as a slightly yellow liquid.

A 4-L glass Erlenmeyer flask was equipped with a Teflon®-coated octagonal stir bar (14 mm × 74 mm) and was supported by a beaker chain clamp. The flask was charged with water (1000 mL) and **3** (1.27 kg, 8.67 mol). Under magnetic stirring (600 rpm), an emulsion was formed. After adding 1.0 kg crushed ice, the mixture cooled to ~ 10 °C. Magnesium oxide (MgO, 174 g, 4.35 mol) was added portion-wise over 15 min to the stirred emulsion creating a white "slurry",[15] which was then allowed to warm to room temperature. The reaction was judged complete by ^{1}H NMR after 3 h. The insoluble MgO is consumed in the reaction creating soluble $MgCl_2$, hence, the white "slurry" eventually turns to an emulsion. The stationary emulsion separated into two phases. With the aid of a funnel, the mixture was poured into a 4-L separatory funnel. The upper aqueous phase is a $MgCl_2$ solution (ca. 2 mol•L^{-1}). The lower phase is virtually pure ESF (ca. 600 mL), which was drained into a 1000 mL Erlenmeyer flask, dried over anhydrous $MgSO_4$ (10 g), and filtered, giving neat **1** (0.85 kg, 7.7 mol). Three 500 mL portions of methylene chloride were used to wash the reaction vessel and the $MgSO_4$ used to dry the neat **1**, and to extract the aqueous phase. The combined organic phase was washed with brine (1 L), dried over anhydrous $MgSO_4$ (50 g), and filtered through a 600-mL sintered glass Buchner funnel. The filtrate was concentrated by rotary evaporation (18 °C, 0.05 bar) to afford an additional 0.10 kg of **1**.[16] Totally, **1** (0.94 kg, 8.6 mol, 98%) was obtained as a slightly yellow liquid, which was judged pure by ^{1}H

NMR. Further short-path distillation under reduced pressure (85 °C, 0.53 bar) helped to remove the color and gave 0.90 kg colorless **1**.

In conclusion, 1.42 kg 2-chloroethanesulfonyl chloride (**2**) was converted to 0.94 kg ethenesulfonyl fluoride (ESF, **1**, 98% overall yield). This interfacial, on-water sequence, which requires little more than stirring and liquid-liquid phase separation, should be practical on a commercial scale. However, our present goal is just to increase access to ESF by the chemical research community.

Experimental Section

Caution! ESF is a toxic substance, which has a pungent odor and strong tear-exciting action. All operations handling ESF and precursors should be performed in a well vented hood. Glassware used in this process should be soaked in 3 mol•L^{-1} NaOH solution or aqueous ammonia overnight to remove any remaining sulfonyl halide (**1**, **2** or **3**) before normal cleaning. John Hyatt and co-workers illustrated that ESF is highly toxic orally and extremely toxic intraperitoneal to laboratory animals. The oral LD_{50} is approximately 50 mg/kg for rats and approximately 10 mg/kg for mice. The intraperitoneal LD_{50} is 1–5 mg/kg for rats and < 5 mg/kg for mice. The liquid was absorbed through the intact skin, the skin absorption LD_{50} is 1–5 mL/kg. The material acts as a severe lachrymator.

*2-Chloroethanesulfonyl fluoride (**3**).* bp 171 °C (1 atm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.94–3.90 (m, 2H), 3.83–3.78 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 52.7 (d, J = 7.2 Hz), 35.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ 56.7. GC-MS t_R = 3.624 min (flow rate 2 mL/min; column

temperature 50 °C for 4 min, then 20 °C/min to 280 °C, then hold 2 min), EI (70 eV)-quadrupole MS calcd for $C_2H_4ClFO_2S$ [M^+] 145.96, m/z (%) 62.0 (70), 63.0 (100), 64.0 (32), 65.0 (32), 67.0 (24), 83.0 (10), 146.0 (0.3).

*Ethenesulfonyl fluoride (***1***).* bp 119 °C (1 atm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 (ddd, J = 16.6, 9.1, 2.1 Hz, 1H), 6.76 (d, J = 16.5 Hz, 1H), 6.47 (dd, J = 9.2, 5.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 134.5 (d, $^3J_{C-F}$ = 3.0 Hz), 130.2 (d, $^2J_{C-F}$ = 28.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ 56.8.

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Associated Content

Supporting Information

The supporting information is available free of charge on the ACS Publications website.

^{1}H, ^{13}C and ^{19}F NMR spectra for compounds **3** and **1**.

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(11) The carboy used in this experiment has a bottom spigot. Which is beneficial for the easy isolation of the desired organic phase without a separatory funnel.

(12) The solubility of potassium bifluoride in water at 20 ºC is 39.2 g/100 mL. The pH of the near saturated potassium bifluoride solution used in this experiment was 3.0, as measured by a pH test strip (1–14 range, 1.0 precision).

(13) Little exotherm was noted. Hence, no heat control is needed, at least at the present scale.

(14) This aqueous solution contained potassium bifluoride [K(FHF), 4.37 mol], potassium dihydrogen trifluoride [K(FHFHF), 8.73 mol], and potassium chloride (KCl, 8.73 mol). The pH of this solution was 1.0, as measured by a pH test strip (1–14 range, 1.0 precision). To minimize fluoride waste, the solution for sulfonyl chloride-fluoride transformation can be regenerated by adding potassium fluoride (508 g, 8.73 mol) to this solution. A rapid exotherm is observed. After cooling to room temperature, the pH of this solution is again 3.0. This regenerated bifluoride solution can be used in the preparation of a new batch of ESF. We found this K(FHF)-K(FHFHF) solution could be used for at least three cycles without apparent change in the effectiveness of the reaction.

(15) Magnesium oxide has poor solubility in water, see: Roy, D. M.; Roy, R. *Am. J. Sci.* **1957**, *255*, 573. Hence, this "slurry" condition approximated "slow addition", which simplifies the operation.

(16) Alternatively, this combined organic phase can be used as a stock solution of ESF in methylene chloride. In this case, it was determined by quantitative NMR that the solution (3.91 kg) contained 0.10 kg ESF. The concentration could be further confirmed by a "titration" using an equimolar reaction between ESF and 1-phenylpiperazine.