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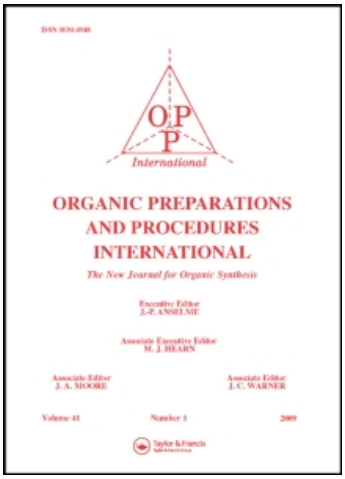

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IMPROVED SYNTHESIS OF FLUOROMETHYL PHENYL SULFONE

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4. E. C. Chapin and J. G. Abramo, *US Patent 3,073,862* (15 January 1963); *CA* , **58**, 13872e (1963).

5. Iodomethane can replace dimethyl sulfate if an efficient condenser is used.

6. R. Asami, *Japan Patent 62 63,595* (20 March 1987); *CA*, **107**, 176631y (1987).

7. The reaction of halides with aqueous solutions of alkali metal cyanides is usually slower than when "dry" conditions are used, presumably due to extensive solvation of the cyanide ion: see C. M. Starks and C. Liotta "Phase Transfer Catalysis: Principles and Techniques", Academic Press, New York, NY, 1978, pp. 93-103.

8. The KCN and $KHCO_3$ were powdered such that >90% of the material would pass through a 125 μ sieve using a Tekmar A-10 mill.

9. (a) G. C. Tustin and R. T. Hembre *J. Org. Chem.*, **49**, 1761 (1984); (b) H. Abbayes, B. Weinberger and G. Tanguy *Tetrahedron Lett.*, **24**, 4005 (1983).

10. The H_2O washes were added to 1500 mL of common bleach to destroy residual KCN.

11. The crown ether may be recovered from this solution by washing with brine, drying ($MgSO_4$), and evaporation.

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IMPROVED SYNTHESIS OF FLUOROMETHYL PHENYL SULFONE

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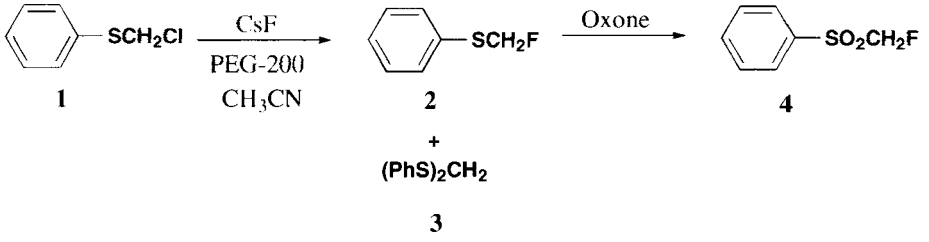
We recently reported a synthesis of fluoromethyl phenyl sulfone (**4**) using the "fluoro-Pummerer" synthesis which employs diethylaminosulfur trifluoride (DAST) as the fluoride source.[1] Compound **4** is an important starting material which we have used for the stereospecific synthesis of terminal vinyl fluorides.[2,3] In addition, this methodology has been applied to the synthesis of



(E)-2'-deoxy-2'-(fluoromethylene)cytidine,[3,4] a mechanism-based inhibitor of ribonucleotide diphosphate reductase which is currently under preclinical evaluation as an antitumor agent. Because of the expense and hazard of using DAST on a large scale, we examined alternate synthetic routes to **4**.

Initial attempts to convert chloromethyl phenyl sulfide (**1**) to the corresponding fluoride (**2**) using KF/18-crown-6[5] resulted in incomplete conversion and/or production of undesired by-product (**3**) after long reaction times (see Table). The use of ammonium phase-transfer agents[6] required longer reaction times and afforded greater amounts of by-products. Similar results were found with the use of KF or KHF_2/polyethylene glycol-200 (PEG-200).[7,8] Attempts to bring about halogen exchange at the sulfoxide oxidation level using KF (4 equiv.)/PEG-200 in dichloroethane (DCE) failed to give any product after 24 hrs at reflux. Reactions using KF in PEG-200/acetonitrile[9] gave inseparable mixtures. Optimum conditions utilized the more reactive fluoride source CsF (2 equiv.) in a homogeneous

TABLE. Conditions for the Conversion of $PhSCH_2Cl$ (**1**) to $PhSCH_2F$ (**2**)

Fluoride Source	Equiv.	Conditions	Reflux Time (hrs)	Products (%)[a] 1	2	3
KF	2	18-crown-6 CH_3CN	96	5	95	0
KF	2	18-crown-6 DMF	96	0	40	60
KF	10	TBA-I CH_2Cl_2/H_2O	240	20	23	27 [b]
KF	10	TBA-I DCE	24	73	24	3
KF	10	TBA-HSO_4 CH_2Cl_2/H_2O	24	56	8	36
KF	10	TBA-Cl CH_2Cl_2/H_2O	3	99	1	0
KF	3	PEG-200 CH_3CN	96	57	29	14
KF	3	PEG-200 DCE	96	6	67	27
KHF_2	4	PEG-200 DCE	4	55	5	40
CsF	4	PEG-200 DCE	6	7	85	8
CsF	2	PEG-200 CH_3CN	1.75	0	100	0

a) % Yields obtained from GC, Conditions: $T_i = 70°$; $t_i = 2$ min; rate = 10°/min; $T_f = 250°$; $t_f = 5$ min. Retention times (min): **1** = 6.2; **2** = 2.4; **3** = 15.1; $PhSCH_2OH$ = 5.9. All crude samples weredissolved on EtOAc and washed with water prior to injection. b) $PhSCH_2OH$ present in 28%.

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solvent mixture of PEG-200/acetonitrile 1/2. After 1.75 hr at 80°, relatively pure product is obtained which is not contaminated with either starting material or by-products. It should be noted that the intermediate fluoromethyl phenyl sulfide (**2**) polymerizes rapidly at room temperature and therefore should either be stored under argon at 0° or immediately oxidized to the corresponding sulfone (**4**) using OXONE[10] in aqueous methanol.

In conclusion, we have found a convenient preparative route to the versatile fluoromethyl phenyl sulfone (**4**) which precludes the use of DAST or crown ethers. This procedure is amenable to the large scale preparation of **4**.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point aparatus and are uncorrected. Proton, fluorine-19 and carbon-13 nuclear magnetic resonance spectra were recorded on a Gemini 300 (300 MHz for ^1H, 282 MHz for ^{19}F and 75 MHz for ^{13}C). TMS (δ 0.0 ppm) was used as an internal reference. GC data was collected from an HP 5790A Series chromatograph with a capillary column: HP1, methyl silicone gum film, 10 m x 0.53 mm, film thickness 2.65 μ. Analytical tlc was performed using 5 cm x 10 cm plates coated with 0.25 mm thickness of silica gel (Kieselgel 60 F_{254}). Chloromethyl phenyl sulfide, CsF (99.9%), PEG-200, and oxone were purchased from Aldrich Chemical Co.

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Fluorormethyl phenyl sulfide (2).- A mixture of chloromethyl phenyl sulfide (**1**) (8.4 mL, 62 mmol), CsF (19.1 g, 130 mmol), and PEG-200/CH_3CN (1:2, 38 mL, dried over molecular sieves) was stirred under a N_2 atmosphere at 80° for 1.75 hrs. Analysis by GC (see Table) showed no remaining chloride **1**. The crude mixture was cooled then partitioned between H_2O (125 mL) and $CHCl_3$ (2 x 125 mL). The combined $CHCl_3$ fractions were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (100 torr, 25-35°) to afford 8.2 g (93%) of the sulfide **2** as a yellow oil. GC: R_t = 2.4 min, (100%.)' bp. 80-90°, 0.1 mm; ^1H NMR ($CDCl_3$): δ 5.72 (d, 2H, J = 52.9), 7.29-7.52 (m, 5H). The colorless oil polymerizes rapidly and therefore no elemental analysis was performed.

Fluoromethyl phenyl sulfone (4).- The crude fluoromethyl phenyl sulfide (**2**) was dissolved in MeOH (85 mL) then cooled to 0° with stirring. A solution of oxone (115.1 g, 190 mmol) in H_2O (85 mL) was added gradually at 0° with stirring. The internal temperature increased to 55°. After cooling to RT, the reaction mixture was stirred for 5 hrs until tlc (3:1 hexane/EtOAc) showed no starting material and no sulfoxide intermediate (sulfoxide R_f = 0.2, sulfone R_f = 0.4). The reaction mixture was filtered on 10 g of celite and the solids rinsed with $CHCl_3$ (3 x 100 mL). Each $CHCl_3$ rinse was used to extract the filtrate. The combined extracts were dried over $MgSO_4$, filtered, then concentrated *in vacuo* (100 torr, 30°). The resulting oil was purified through vacuum distillation (115-132°, 1-2 torr). Crystallization occurred upon cooling to RT to afford 7.6 g (70% overall yield) **4** as a white crystalline solid, mp 47-48.5°. Upon recrystallization from hexane (75 mL) the mp. was raised to 53-55°, lit.[11] mp. 50-51°; ^1H NMR: δ 8.0-7.9 (m, 2H), 7.8-7.7 (m,1H), 7.7-7.6 (m, 2H), 5.16 (d, 2H, J = 49.3 Hz); ^{13}C NMR: δ 136.08, 135,05, 129.71, 129.16, 92.01 (d, J = 218.8 Hz); ^{19}F NMR: δ -211.27 (t, J = 47.1Hz).

Anal. Calcd. for $C_7H_7FO_2S$: C, 48.26; H, 4.05. Found: C, 48.35; H, 3.94

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AN EFFICIENT ONE STEP SYNTHESIS OF *tert*-BUTYL GLYCINATE AND *tert*-BUTYL SARCOSINATE

Submitted by (04/11/94)

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tert-Butyl esters are widely used as an acid-labile protection for carboxylic acids in amino