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Straightforward and Scalable Synthesis of Diethyl Fluoro-(phenylsulfonyl)methylphosphonat

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STRAIGHTFORWARD AND SCALABLE SYNTHESIS OF DIETHYL FLUORO(PHENYLSULFONYL)METHYLPHOSPHONATE

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Abstract: A process is described for the synthesis of diethyl fluoro(phenylsulfonyl)methylphosphonate which is easily and safely performed on a multi-kilogram scale.

Diethyl fluoro(phenylsulfonyl)methylphosphonate (**1**) has great utility for the stereospecific Horner-Emmons synthesis of terminal vinyl fluorides. McCarthy, et al. have demonstrated the usefulness of **1**, formed *in-situ*, in the synthesis of α-fluoro-α,β-unsaturated sulfones from aldehydes and ketones.[1,2,3] We were interested in the use of isolated **1** in the optimization of the Horner-Emmons synthesis of (*E*)-2'-deoxy-2'-(fluoromethylene)cytidine (**2**), a mechanism-based inhibitor of ribonucleotide diphosphate reductase, which is currently under preclinical evaluation as an anti-tumor agent.[2,3]

Two references to the synthesis and isolation of diethyl fluoro-(phenylsulfonyl)methylphosphonate have appeared in the literature.[4,5] In both cases, the potassium salt of diethyl (phenylsulfonyl)methylphosphonate (**4**) was treated with an electrophilic fluorinating reagent. However, the electrophilic fluorinating reagents used were either too hazardous ($FClO_3$)[4] or expensive

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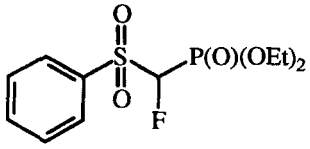

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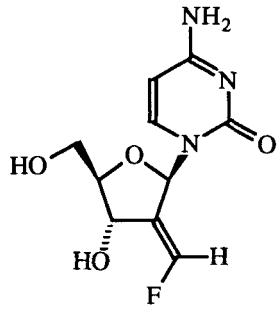
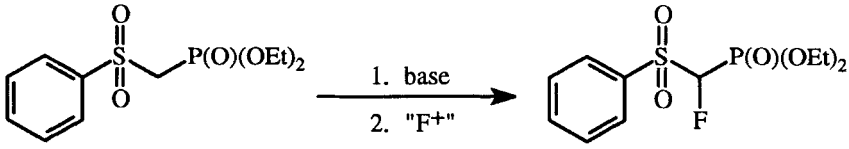


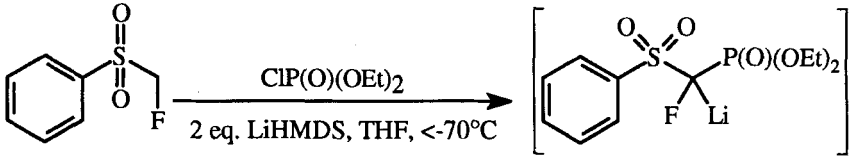
2

(SELECTFLUOR^{TM})[5] for use on large-scale. Therefore, we investigated the optimization and isolation of **1** from the procedure used previously to form **1** *in-situ*.



4 **1**

In the procedure for the *in-situ* formation of **1**,[1] two equivalents of lithium bis(trimethylsilyl)amide (LiHMDS) were added to a solution of fluoromethyl phenyl sulfone[6] (**3**) and diethyl chlorophosphate[7] in THF cooled to less than -70°C.



3

The carbanion of **1** thus formed was treated with a variety of aldehydes and ketones affording vinyl fluorides in good to excellent yields. To perform the isolation of **1** from the base-induced coupling of **3** and diethyl chlorophosphate, base selection, reagent stoichiometry and isolation parameters were optimized.

Butyllithium and lithium diisopropylamide were investigated as less-expensive alternatives to LiHMDS. In a typical procedure, base was added dropwise to a mixture of fluoromethyl phenyl sulfone and diethyl chlorophosphate, keeping the internal temperature below -65 °C, followed by warming to 0 °C and

quenching with aqueous ammonium chloride or acetic acid. Isolated yields in all three cases were nearly identical. However, butyllithium was more desirable due to ease of work-up and reduced color production.

Complete consumption of fluoromethyl phenyl sulfone was never attained in the coupling reaction. Typically 5-10 area% (GC) of **3** remained after the reaction, even with a 20% excess of diethyl chlorophosphate.[8] Additional base and/or diethyl chlorophosphate did not increase conversion.[9]

Isolation of **1** from the coupling of fluoromethyl phenyl sulfone and diethyl chlorophosphate involved removal of the aqueous phase, chemical drying of the organic phase, concentration and crystallization from a suitable solvent. *t*-Butyl methyl ether or diethyl ether/hexane gave good recoveries of **1** but left significant colored material in the solid. The best quality and recovery was obtained by crystallization from a 2:1 mixture of toluene and heptane at -20 °C. Using these conditions, isolated yields of **1** ranged from 66% to 73% with purity greater than 99% (GC).

In conclusion, a procedure has been demonstrated for the synthesis of diethyl fluoro(phenylsulfonyl)methylphosphonate (**1**) *via* base-induced coupling of fluoromethyl phenyl sulfone and diethyl chlorophosphate. This method is superior in yield and economy to those described previously.[4,5] To date, this procedure has been used to synthesize multi-kilogram quantities of **1** safely and efficiently.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and were uncorrected. Proton NMR spectra (300 MHz) were referenced to tetramethylsilane (δ 0.00 ppm). Carbon NMR spectra (75 MHz) were referenced to the center line of the $CDCl_3$ triplet (δ 77.00 ppm). Fluorine-19 NMR spectra 564 MHz) were referenced to $CFCl_3$ (δ 0.00 ppm). Phosphorus-31 NMR spectra (242 MHz) were referenced to 85% H_3PO_4 (δ 0.00 ppm). Infrared spectra of neat **1** were collected on a Nicolet 510M FT-IR spectrophotometer. Gas chromatographic (GC) data were collected with an HP 5890 Series II chromatograph with a DB-5 capillary column (30 m x 0.25 mm, film thickness 0.25 μm). Butyllithium (1.6 M) and diethyl chlorophosphate were purchased from the Aldrich Chemical Co. Diethyl chlorophosphate was distilled before use.[7] Fluoromethyl phenyl sulfone (**3**) was synthesized as reported recently.[6]

Diethyl Fluoro(phenylsulfonyl)methylphosphonate:

Fluoromethyl phenyl sulfone (0.490 kg, 2.813 mol) and distilled diethyl chlorophosphate (0.577 kg, 3.343 mol) were dissolved in tetrahydrofuran (4.299 kg, dried over 4Å molecular sieves) at room temperature. The solution was cooled to -75 °C (external dry ice/isopropanol bath). Butyllithium (2.354 kg, 3.766 mol, 1.6M solution in THF) was added to the chilled reaction mixture over 6 hours. The maximum internal temperature during the addition was -66 °C. The muddy-brown mixture was then post-reacted at less than -70 °C for 1.5 hours and then warmed to -45 °C over one hour. The reaction mixture was quenched into a well-stirred solution of ammonium chloride (0.464 kg) in water (3.849 kg). The quenched mixture was stirred for 0.5 hours then allowed to stand overnight. The organic (top) and aqueous (bottom) phases were separated and the aqueous phase was extracted with ethyl acetate (1.117 kg). The aqueous (bottom) phase was drained and discarded. The original organic phase was combined with the ethyl acetate organic phase and dried with magnesium sulfate. This mixture was vacuum filtered and the resulting salt cake was rinsed with toluene (0.825 kg). The filtrate was concentrated in a rotary evaporator *in vacuo* (< 40 mmHg) at 40 °C. Toluene (0.956 kg) was added to the residue and this was evaporated to a constant weight under the same conditions. The yellow-tan, semi-solid residue (0.956 kg) was dissolved in toluene (1.476 kg) and diluted with heptane (0.670 kg). The homogeneous mixture was cooled to 10 °C, seeded with crystals of pure **1** (approx 10 mg), and slowly cooled to -20 °C. Crystallization began at about 5 °C. The mixture was stirred at -20 °C for two hours to complete crystallization. The crystalline slurry was vacuum filtered, and the resulting filter cake was washed with a mixture of toluene (0.392 kg) and heptane (0.682 kg). The remaining white filter cake was dried under a stream of nitrogen to a constant weight. The remaining solid (0.638 kg, 73% yield) was pure diethyl fluoro(phenylsulfonyl)methylphosphonate (**1**) by GC (>99 area%). **mp**. 63-64 °C (lit.[4] mp. 64 °C). **^{1}H-NMR** ($CDCl_3$) δ 7.96 (m, 2H), 7.67 (m, 1H), 7.56 (m, 2H), 5.36 (dd, $^2J_{HF}$=46Hz, $^2J_{HP}$=6.6Hz, 2H), 4.24 (m, 4H), 1.30 ppm (t, J=7Hz, 6H). **^{13}C-NMR** ($CDCl_3$) δ 136.3, 134.9, 129.7, 129.1, 97.5 ($^1J_{CF}$=230Hz, $^1J_{CP}$=175Hz), 64.8, 16.2 ppm. **^{19}F-NMR** ($CDCl_3$) δ -194.2 ppm ($^2J_{PF}$=67Hz). **^{31}P-NMR** ($CDCl_3$) δ 5.69 ppm ($^2J_{PF}$=67Hz). **IR** (neat) ν 2989, 2917, 1339, 1269, 1021. **HRMS** (CI): Calcd. (MH^+) 311.0518; Found 311.0510. ***Anal.*** Calcd. for $C_{11}H_{16}FO_5PS$: C, 42.6%; H, 5.20%; F, 6.1%; O,

25.8%; P, 10.0%; S, 10.3%. Found: C, 42.7%; H, 5.04% (combustion); F, 5.6%; O, 27.7%; P, 10.6% (neutron activation); S, 9.5% (X-ray fluorescence).

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7. Diethyl chlorophosphate is a highly toxic and potent acetylcholinesterase inhibitor and should be handled with great care (Material Safety Data Sheet, The Aldrich Chemical Co., 1993).
8. Excess butyllithium and diethyl chlorophosphate only gave more butyl diethylphosphonate, the product of attack of butyllithium on diethyl chlorophosphate.
9. Phosphonate **1** is unstable to hydroxide and it is suspected that most or all of the fluoromethyl phenyl sulfone remaining in the reaction was formed during the quenching procedure with aqueous ammonium chloride.

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