Stannyl Radical-Mediated Cleavage of \( \pi \)-Deficient Heterocyclic Sulfones. Synthesis of \( \alpha \)-Fluoro Esters and the First Homonucleoside \( \alpha \)-Fluoromethylene Phosphonate

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Received October 19, 1995

Phosphonate derivatives of nucleosides have been studied extensively as analogues of biologically important nucleotides.\(^1\) Blackburn proposed that \( \alpha \)-fluoro and \( \alpha,\alpha \)-diluoro substitution on monophosphate esters should provide superior phosphate ester surrogates (closer isosteres and isopolar parallels).\(^2,3\) The bridging oxygen in di- and triphosphates has been replaced with a fluoromethyl group.\(^5\) Condensations of OS\(^-\)-activated nucleosides\(^6\) and activated \( \alpha \)-monophosphonomethylenes\(^6\) with (fluoromethylen)- and (diluoromethylen)bisphosphonic acids have given di- and triphosphate analogues with \( \alpha \) and \( \beta \) pyrophosphate oxygen replaced with CHF and CF\(_2\) units. Phosphonate homologues of nucleotides (OS\(^-\)-activated nucleosides)\(^7\) are of current interest since they are not substrates for the usual phosphatases. Established syntheses of homophosphonates with CH\(_2\) units employed Wittig\(^7\) or Arbuzov\(^8\) chemistry. Recent reports\(^9,10\) of their CF\(_2\) analogues have utilized coupling of nucleic acid bases with a previously synthesized \( \alpha,\alpha \)-diluorohomoribose phosphonate derivative\(^11\) or a carbonyl analogue.\(^10\) The \( \alpha,\beta \)-Fluoromethylenebisphosphonic acid\(^12\) has been shown to exert potent inhibition of uridine triphosphatase.\(^2\)

\( \alpha \)-Fluoro- and \( \alpha,\beta \)-diluorohomophosphonates have been prepared by Arbuzov reactions with fluorohalomethanes,\(^13\) and \( \alpha,\beta \)-diluoroheteroaryl phosphonates\(^14\) are of current interest since they are not substrates for the usual phosphatases. Fluorinated analogues of nucleosides with CHF and CF\(_2\) units have been used in medicinal chemistry and biochemistry.\(^15\)

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(21) Nicholls, D. J., 80, 1155–1157.
(tetrfluoroborate)\textsuperscript{18} gave the desired \(\alpha\)-fluoro sulfone phosphonate \textit{4a}, which was debenzoylated and purified to give \textit{4b}\textsuperscript{22} (47\% from \textit{3b}).

Standard procedures\textsuperscript{24} for removal of sulfonyl groups \[\text{e.g., treatment of \textit{4b} with Al(Hg) or Na(Hg)}\] or base-promoted elimination\textsuperscript{240–d} failed to give \textit{5a} or its 5′,6′-unsaturated analogue. Although tributylstannane is used routinely for hydrogenolysis of carbon–halogen, carbon–sulfur, carbon–selenium, and carbon–nitro bonds,\textsuperscript{25} it is ineffective for cleavage of typical saturated sulfones. In contrast, stannodesulfonylations of vinyl sulfones (including nucleoside examples \textit{26b,c}) are known, and saturated sulfones. In contrast, stannodesulfonylations of vinyl sulfones \[\text{e.g., stannodesulfonylation/protiodestannylation (\textit{4b}) with EtOAc/KF/H}_2\text{O (5 mL/30 mg/0.3 mL). The mixture was evaporated, then the residue was chromatographed (silica, pentane} \times \text{3% EtOAc/pentane)}\] might involve successive stannodesulfonylation/protiodestannylation at the “vinyllic” C2–C3 bond of the pyrrole ring. Desulfonylations of allylic sulfones\textsuperscript{26} with tributylstannane are known, and sulfonyl radicals are versatile intermediates in organic synthesis.\textsuperscript{27} Therefore, we began an investigation of radical-mediated cleavage of \(\pi\)-deficient aryl sulfones.

Ethyl hexanoate was chosen as a model for diethyl alkylphosphonates in which C2 would simulate the phosphonate \(\pi\)-carbon. Treatment of ethyl 2-bromohexanoate (\textit{7}, Scheme 2) with pyridine-2-thione, pyrimidine-2-thione, and benzenethiol \[\text{e.g., thiolation at the “vinylic” C2–C3 bond of the pyrrole ring. Desulfonylations of allylic sulfones} \textit{26} with tributylstannane are known, and sulfonyl radicals are versatile intermediates in organic synthesis.\textsuperscript{27} Therefore, we began an investigation of radical-mediated cleavage of \(\pi\)-deficient aryl sulfones. Ethyl hexanoate was chosen as a model for diethyl alkylphosphonates in which C2 would simulate the phosphonate \(\pi\)-carbon. Treatment of ethyl 2-bromohexanoate (\textit{7}, Scheme 2) with pyridine-2-thione, pyrimidine-2-thione, and benzenethiol in solutions of NaH/THF/DMF gave the respective ethyl 2-(arylthio)hexanoates in excellent yields. Oxidation gave the corresponding sulfones \textit{8a,b}\textsuperscript{22} and \textit{8c}\textsuperscript{23a}.

Treatment of ethyl 2-(phenylsulfonyl)hexanoate \textit{8c} with Bu\textsubscript{3}SnH/AlBN/benzene at reflux for 48 h caused no observed change in the starting material. However, parallel treatment of ethyl 2-(pyridin-2-ylsulfonyl)hexanoate \textit{8a} for 36 h gave ethyl hexanoate \textit{10a} (60\%) plus unchanged \textit{8a} and minor decomposition products. Analogous treatment of ethyl 2-(pyrimidin-2-ylsulfanyl)hexanoate \textit{8b} gave complete conversion to \textit{10a} within 1 h. Substitution of BuSnD for BuSnH gave ethyl 2-deuteriohexanoate \textit{10b}.

Carbanion-mediated fluorinations proceeded smoothly in the model series. The 2-(pyridin-2-ylsulfanyl) \textit{8a} and 2-(pyrimidin-2-ylsulfanyl) \textit{8b} esters were treated with potassium hydride, and the enolates were quenched with Selectfluor to give ethyl 2-fluoro-2-(pyridin-2-ylsulfanyl)hexanoate \textit{22} (9a) and ethyl 2-fluoro-2-(pyrimidin-2-ylsulfanyl)hexanoate \textit{22} (9b) in high yields. Tributylstannane-mediated desulfonylation of \textit{9a} (28 h) and \textit{9b} (1 h) gave ethyl 2-fluorohexanoate \textit{23b} (10c; 60\% and 95\%, respectively). Treatment of \textit{9b} with BuSnD gave 2-\textit{[H]}-10c.\textsuperscript{22} These reactions\textsuperscript{30} provide convenient access to biologically important \(\alpha\)-fluorocarbonyl compounds\textsuperscript{31} and their isotope-labeled derivatives. \(\pi\)-Deficient heterocyclic sulfones could be especially advantageous in reactions that involve generation of sulfonyl carbanions since acidifying effects of these pyridine and pyrimidine 2-ylsulfanyl groups on \(\pi\)-carbon are greater than that of the phenylsulfonyl group.

This methodology for sulfonyl removal was successful for our target nucleoside phosphate. Treatment of \textit{4b} with BuSnH/AlBN/benzene/\textit{Air} caused cleavage of the sulfonyl linkage \[\textit{5a} (61\%), and removal of the isopropyridine group and RP-HPLC (H\textsubscript{2}O/CH\textsubscript{3}CN; 19:1) gave pooled fractions of \textit{5b}\textsuperscript{22} enriched in each of the two 6′-fluoro diastereomers \[\sim 12:1 \text{ vs } \sim 1:6\]. Independent treatment of the enriched diastereomer mixtures with trimethylsilyl bromide and purification (DEAE Sephadex A-25; 0.01 → 0.20 M TEAB/H\textsubscript{2}O) followed by conversion to the sodium salts [Dowex 50 × 8(\text{H}\textsuperscript{+})] and then Na\textsuperscript{+}]: H\textsubscript{2}O gave 6′-deoxy-6′-fluorohexanoate \textit{21} \textsuperscript{6-phosphonato}–homouridine disodium salt\textsuperscript{22} (6).

In summary, we have developed convenient and efficient methodologies for synthesis of carboxylate and phosphate heterocyclic \(\alpha\)-sulfones, their \(\alpha\)-fluorination with Selectfluor, and their desulfonylation with tributylstannane. This provides a facile new route for the preparation of \(\alpha\)-[\textit{[H]}] and \(\alpha\)-fluoro-\[\textit{[H]}\] carbonyl compounds and phosphonates. Barton thio-hydroxamic ester chemistry was used to prepare a protected 6′-(pyridin-2-ylthio)–homouridine phosphate that was oxidized (m-CPPA) to the sulfur, fluorinated (Selectfluor), desulfonylated (BuSnH/AlBN), and deprotected to give the first reported 6′-deoxy-6′-fluorohomouridine 6′-phosphonate.

**Acknowledgment.** We thank the American Cancer Society (Grant DHP-34) and Brigham Young University development funds for support, Air Products for a gift of Selectfluor reagent, and Mrs. Jeanny Gordon for assistance with the manuscript. We also thank Professor Stefan Kinastowski and the Academy of Agriculture, Poznan, Poland, for extensions of a faculty leave for S.F.W.