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Stannyl Radical-Mediated Cleavage of π-Deficient Heterocyclic Sulfones. Synthesis of α-Fluoro Esters and the First Homonucleoside α-Fluoromethylene Phosphonate[1]

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Phosphonate derivatives of nucleosides have been studied extensively as analogues of biologically important nucleotides.[2,3] Blackburn proposed that α-fluoro and α,α-difluoro substitution on methylenephosphonates should provide superior phosphate ester surrogates (closer isosteric and isopolar parallels).[3,4] The bridging oxygen in di- and triphosphates has been replaced with mono- and difluoromethylene entities,[3−5] and the OH function on phosphates has been replaced with a fluoromethyl group.[6] Condensations of O5′-activated nucleosides[5a] and activated 5′-monophosphates[4a] with (fluoromethylene)- and (difluoromethylene)bis(phosphonic acids) have given di- and triphosphate analogues with α and β pyrophosphate oxygen replaced with CHF and CF_2 units. Phosphonate homologues of nucleotides (O5′ replaced with CH_2,[7] CHF,[8] or CF_2[9]) are of enhanced interest since they are not substrates for the usual phosphatases. Established syntheses of homophosphonates with CH_2 units employed Wittig[7] or Arbuzov[2] chemistry. Recent reports[9,10] of their CF_2 analogues have utilized coupling of nucleic acid bases with a previously synthesized α,α-difluorohomoribose phosphonate derivative[11] or a carbocyclic analogue.[10] The 9-(5,5-difluoro-5-phosphonopentyl)guanine congener of acyclovir phosphate was found to exert potent inhibition of purine nucleoside phosphorylase.[12]

α-Fluoro- and α,α-difluoromethylenephosphonates have been prepared by Arbuzov reactions with fluorohalomethanes,[13] fluorination of phosphonate-stabilized anions,[14] alkylation of [(diethoxyphosphoryl)difluoromethyl]lithium,[15] and palladium-catalyzed addition of diethyl (difluoroiodomethyl)phosphonate to alkenes.[16] Fluorinations of sulfonyl-stabilized phosphonate carbanions with perchloryl fluoride[17] and the new Selectfluor reagent[18] have been described. We employed Barton's chain-extension method with diethyl vinylphosphonate and a protected uridine 5′-thiohydroxamic ester to obtain the 6′-(pyridin-2-yl) thioether. Its oxidation (*m*-CPBA) and fluorination of the derived sulfonyl-stabilized carbanion (Selectfluor) were successful. However, attempted desulfonylation by known procedures failed. We now have discovered that pyridin-2-yl- and especially pyrimidin-2-ylsulfonyl groups undergo cleavage from the α-carbon atoms of carboxylic and phosphonic esters. This new methodology was employed for the first reported synthesis of a 6′-deoxy-6′-fluorohomonucleoside phosphonate from uridine.

Treatment of 2′,3′-*O*-isopropylideneuridine 5′-carboxylic acid[19] (**1**, Scheme 1) with isobutyl chloroformate/*N*-methylmorpholine/THF and the sodium salt of *N*-hydroxypyridine-2-thione gave the *N*-hydroxypyridine-2-thioester. Photolysis (tungsten light) with diethyl vinylphosphonate gave the reported addition product **2**[20a,b] (∼60%) plus byproducts.[20c,d] Attempted C6′ fluorination of thioether **2** with (diethylamino)sulfur trifluoride (DAST)[21a] or oxidation of **2** and treatment of the sulfoxides with DAST/$SbCl_3$[21b] failed. Oxidation of **2** with >2 equiv of *m*-CPBA gave the pyridin-2-yl sulfone **3a**, which was benzoylated at N3 to give **3b**.[22] Treatment of **3b** with potassium hydride generated a stabilized C6′ carbanion. Several "positive fluorine" sources failed to give defined products, but Selectfluor [1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis-

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(22) NMR ($CDCl_3$, unless specified). (a) Data as reported for **8c**[23a] and **10c**.[23b] (b) **3b**: ^{1}H NMR δ 1.25 (t, J = 7.0 Hz, 6), 1.31 (s, 3), 1.52 (s, 3), 2.40−2.71 (m, 2), 4.10 (q, J = 7.0 Hz, 4), 4.38−4.71 (m, 3), 4.96−5.12 (m, l), 5.58 (d, J = 1.1 Hz, 0.5, Hl′), 5.67 (d, J = 1.5 Hz, 0.5, Hl′), 5.83 and 5.85 (d and d, J = 8.1 Hz, 0.5 and 0.5), 7.37 and 7.39 (d and d, 0.5 and 0.5), 7.45−8.14 (m, 8), 8.67−8.94 (m, l); HRMS (CI) *m/z* 664.1724 (100, MH^+ $[C_{29}H_{35}N_3O_{11}PS]$ = 664.1730). (c) **4b**: δ 1.24−1.35 (m, 9), 1.51 and 152 (2s, 3), 2.71−3.06 (m, 2), 4.16−4.32 (m, 4), 4.68−4.76 (m, 2), 4.96 (dd, $J_{2'-3'}$ = 6.3 Hz, $J_{2'-1'}$ = 2.0 Hz, 0.5, H2′), 4.99 (dd, $J_{2'-3'}$ = 5.9 Hz, $J_{2'-1'}$ = 2.0 Hz, 0.5, H2′), 5.48 and 5.49 (2d, 1, H1′), 5.68 and 5.71 (2dd, J_{5-6} = 8.2 Hz, $J_{5\text{-}NH}$ = 2.3 Hz, 1, H5), 7.19 and 7.22 (2d, 1, H6), 7.60, 7.97, 8.14, 8.79 (4m, 4), 9.06 (br s, 1); ^{19}F NMR δ −168.2 (ddd, J_{F-P} = 82.2 Hz, $J_{F-5',5''}$ = 30.0, 17.1 Hz, 0.5), −168.6 (ddd, J_{F-P} = 82.2 Hz, $J_{F-5',5''}$ = 29.1, 17.1 Hz), plus minor 4′(*S*) signals; HRMS (CI) *m/z* 578.1367 (100, MH^+ $[C_{22}H_{30}FN_3O_{10}PS]$ = 578.1374). (d) **5b** (faster isomer): ^{1}H NMR (D_2O) δ 1.23 (t, J = 6.9 Hz, 6), 2.22−2.36 (m, 2), 4.03 (t, J = 5.9 Hz, 1), 4.08−4.12 (m, 1), 4.15 (q, 4), 4.27 (t, J = 3.9 Hz, 1), 5.14 (dm, $J_{6'-F}$ = 45.2 Hz, 1), 5.67 (d, $J_{1'-2'}$ = 3.3 Hz, 1), 5.76 (d, J_{5-6} = 8.2 Hz, 1) 7.52 (d, 1); ^{19}F NMR (D_2O) δ −203.2 (dddd, J_{F-P} = 78.2 Hz, $J_{F-6'}$ = 46.1 Hz, $J_{F-5',5''}$ = 28.3, 10.5 Hz); HRMS (CI) *m/z* 397.1170 (100, MH^+ $[C_{14}H_{23}FN_2O_8P]$ = 397.1176). (e) **6** (from faster **5b**): mp 200−210 °C dec; UV (H_2O) max 262 nm (ϵ 8200), min 231 nm (ϵ 2100); ^{1}H NMR (D_2O) δ 2.11−2.22 (m, 2), 4.04 (t, J = 6.0 Hz, 1), 4.15 (q, J = 6.2 Hz, 1), 4.25 (t, J = 5.0 Hz, 1), 4.83 (dm $J_{6'-F} \approx$ 46 Hz, 1), 5.75 (d, $J_{1'-2'}$ = 4.5 Hz, 1), 5.88 (d, J_{5-6} = 8.0 Hz, l), 7.59 (d, 1); ^{19}F NMR (NaH/D_2O) δ −200.5 (dddd, J_{F-P} = 61.9 Hz, $J_{F-6'}$ = 48.2 Hz, $J_{F-5',5''}$ = 27.3, 9.1 Hz); HRMS (FAB) *m/z* 385.0194 (76, MH^+ $[C_{10}H_{13}FN_2O_8PNa_2]$ = 385.0189), 363.0370 (35, MH^+ $[C_{10}H_{14}FN_2O_8PNa]$ = 363.0370). (f) **8a** (oil): ^{1}H NMR similar to **8b**. Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.63; H, 6.52; N 5.09. (g) **8b**: mp 50−51 °C; ^{1}H NMR δ 0.90 (t, J = 6.6 Hz, 3), 1.1 (t, J = 7.1 Hz, 3), 1.28−1.51 (m, 4), 2.15−2.28 (m, 2), 4.10 (q, 2), 4.61 (dd, J = 6.2, 8.7 Hz, 1), 7.60 (t, J = 4.9 Hz, 1), 8.97 (d, 2). Anal. Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.33; H, 6.34; N, 9.78. Found: C, 50.33; H, 6.15; N, 9.60. (h) **9a** (oil): ^{1}H NMR δ 0.90 (t, J = 6.8 Hz, 3), 1.16−1.52 (m, 7), 2.30−2.73 (m, 2), 4.31 (q, J = 7.2 Hz, 2), 7.60 (ddd, J = 1.4, 4.7, 7.6 Hz, 1), 7.98 (dt, J = 1.7, 7.6 Hz, 1), 8.09 (dt, J = 1.1 Hz, 7.8 Hz, 1), 8.73 (ddd, J = 1.0, 1.7, 4.8 Hz, 1); ^{19}F NMR δ −159.4 (dd, J = 10.3, 38.5 Hz). Anal. Calcd for $C_{13}H_{18}FNO_4S$: C, 51.47; H, 5.98; N, 4.62. Found: C, 51.39; H, 6.12; N, 4.51. (i) **9b** (oil): ^{1}H and ^{19}F NMR similar to **9a**. Anal. Calcd for $C_{12}H_{17}FN_2O_4S$: C, 47.36; H, 5.63; N, 9.20. Found: C, 47.57; H, 5.72; N, 9.19. (j) 2-[^{2}H]-**10c**: ^{1}H NMR same as **10c**[23b] except simplification at δ 1.87 and small signals (∼10%) at δ 4.86; ^{19}F NMR δ −193.2 (tt, J_{F-D} = 7.9 Hz, J_{F-H} = 24.9 Hz).

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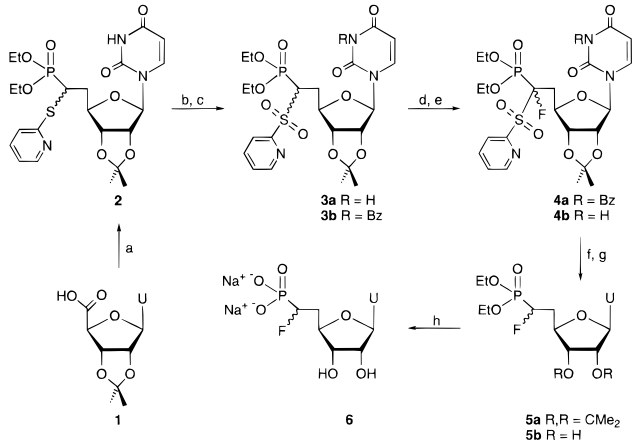
Scheme 1[a]



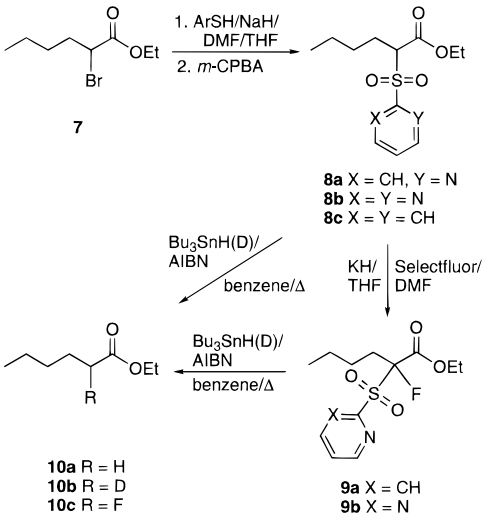
[a] (a) (i) Isobutyl chloroformate/*N*-methylmorpholine/THF; (ii) sodium salt of *N*-hydroxypyridine-2-thione; (iii) diethyl vinylphosphonate/$h\nu$. (b) *m*-CPBA. (c) BzCl/EtN(*i*-Pr)$_2$/pyridine. (d) KH/THF/Selectfluor/DMF. (e) NH_3/MeOH. (f) Bu_3SnH/AIBN/benzene/Δ. (g) TFA/H_2O. (h) (i) Me_3SiBr/DMF; (ii) DEAE Sephadex; (iii) Dowex 50 × 8(H^+) then (Na^+).

(tetrafluoroborate)][18] gave the desired α-fluoro sulfone phosphonate **4a**, which was debenzoylated and purified to give **4b**[22] (47% from **3b**).

Standard procedures[24] for removal of sulfonyl groups [*e.g.*, treatment of **4b** with Al(Hg) or Na(Hg); or base-promoted elimination[24b−d]] failed to give **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,[25] it is ineffective for cleavage of typical saturated sulfones. In contrast, stannodesulfonylations of vinyl sulfones[26] (including nucleoside examples[26b,c]) are known, and recent desulfonylations of 2-(alkyl- and -aryl)sulfonylpyrroles[27] might involve successive stannodesulfonylation/protiodestannylation at the "vinylic" C2−C3 bond of the pyrrole ring. Desulfonylations of allylic sulfones[28] with tributylstannane are known, and sulfonyl radicals are versatile intermediates in organic synthesis.[29] Therefore, we began an investigation of radical-mediated cleavage of π-deficient aryl sulfones.

Ethyl hexanoate was chosen as a model for diethyl alkylphosphonates in which C2 would simulate the phosphonate α-carbon. Treatment of ethyl 2-bromohexanoate (**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 **8a,b**[22] and **8c**.[23a] Treatment of ethyl 2-(phenylsulfonyl)hexanoate (**8c**) with Bu_3SnH/AIBN/benzene

Scheme 2



at reflux for 48 h caused no observed change in the starting material. However, parallel treatment of ethyl 2-(pyridin-2-ylsulfonyl)hexanoate (**8a**) for 36 h gave ethyl hexanoate (**10a**, 60%) plus unchanged **8a** and minor decomposition products. Analogous treatment of ethyl 2-(pyrimidin-2-ylsulfonyl)hexanoate (**8b**) gave complete conversion to **10a** within 1 h. Substitution of Bu_3SnD for Bu_3SnH gave ethyl 2-deuteriohexanoate (**10b**).

Carbanion-mediated fluorinations proceeded smoothly in the model series. The 2-(pyridin-2-ylsulfonyl) **8a** and 2-(pyrimidin-2-ylsulfonyl) **8b** esters were treated with potassium hydride, and the enolates were quenched with Selectfluor to give ethyl 2-fluoro-2-(pyridin-2-ylsulfonyl)hexanoate[22] (**9a**) and ethyl 2-fluoro-2-(pyrimidin-2-ylsulfonyl)hexanoate[22] (**9b**) in high yields. Tributylstannane-mediated desulfonylation of **9a** (28 h) and **9b** (1 h) gave ethyl 2-fluorohexanoate[23b] (**10c**; 60% and 95%, respectively). Treatment of **9b** with Bu_3SnD gave 2-[^{2}H]-**10c**.[22] These reactions[30] provide convenient access to biologically important α-fluorocarbonyl compounds[31] and their isotope-labeled derivatives. π-Deficient heterocyclic sulfones could be especially advantageous in reactions that involve generation of sulfonyl carbanions since acidifying effects of these pyridin- and pyrimidin-2-ylsulfonyl groups on α-carbon are greater than that of the phenylsulfonyl group.

This methodology for sulfone removal was successful for the synthesis of our target nucleoside phosphonate. Treatment of **4b** with Bu_3SnH/AIBN/benzene/Δ/48 h caused cleavage of the sulfonyl linkage (**5a**, 61%), and removal of the isopropylidene group and RP-HPLC (H_2O/CH_3CN; 19:1) gave pooled fractions of **5b**[22] enriched in each of the two 6′-fluoro diastereomers (∼12:1 *vs* ∼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_2O) followed by conversion to the sodium salts [Dowex 50 × 8(H^+) and then (Na^+); H_2O] gave 6′-deoxy-6′-fluoro-6′-(phosphonato)-homouridine disodium salt[22] (**6**).

In summary, we have developed convenient and efficient methodologies for synthesis of carboxylate and phosphonate heterocyclic α-sulfones, their α-fluorination with Selectfluor, and their desulfonylation with tributylstannane. This provides a facile new route for the preparation of α-[$^{2/3}$H] and α-fluoro-α-[$^{2/3}$H] carbonyl compounds and phosphonates. Barton thiohydroxamic ester chemistry was used to prepare a protected 6′-(pyridin-2-ylthio)homouridine phosphonate that was oxidized (*m*-CPBA) to the sulfone, fluorinated (Selectfluor), desulfonylated (Bu_3SnH/AIBN), and deprotected to give the first reported 6′-deoxy-6′-fluorohomonucleoside 6′-phosphonate.

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(30) Typical procedure: Ar was bubbled through **9b** (304 mg, 1 mmol)/benzene (5 mL) for 1 h, and Bu_3SnH (0.537 mL, 582 mg, 2.0 mmol) was added. Deoxygenation was continued for 15 min, AIBN (33 mg, 0.2 mmol) was added, and the solution was refluxed for 1 h (TLC). Volatiles were evaporated (<25 °C, ∼20 mmHg) and the residue was stirred overnight with EtOAc/KF/H_2O (5 mL/30 mg/0.3 mL). The mixture was evaporated, and the residue was chromatographed (silica, pentane → 3% EtOAc/pentane) to give **10c**[23b] (154 mg, 95%).

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