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A NEW ROUTE TO 2-FLUORO-1-OLEFINS UTILIZING A SYNTHETIC EQUIVALENT FOR THE 1-FLUOROETHENE ANION

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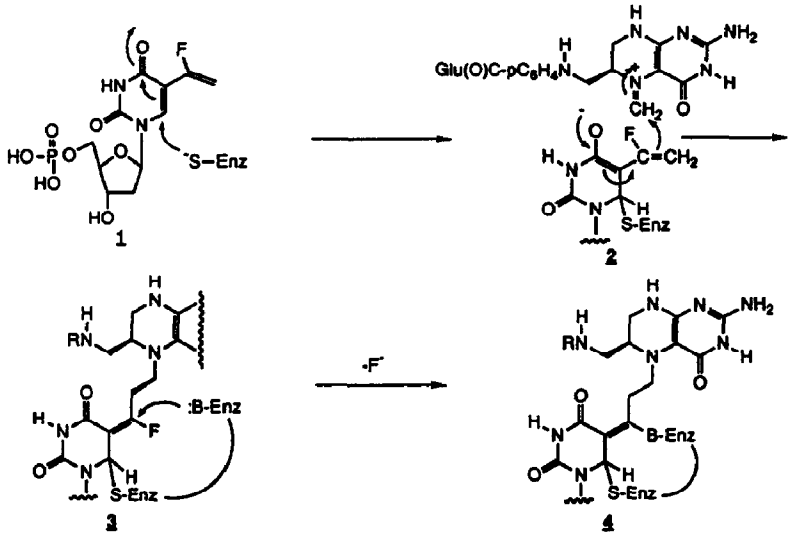
Abstract: The preparation of (E)-tributyl(1-fluoro-2-trimethylsilyl)vinylstannane (10), a synthetic equivalent for the 1-fluoroethene anion, and its utility for the synthesis of nucleoside 20, and other 2-fluoro-1-olefins is described.

Recently, we reported a route to 2-fluoro-1-olefins which relied on the addition of phenylselenium fluoride to terminal olefins and ozonolysis of the intermediate β-fluoro phenylselenides.[1,2] An alternative route to this class of compounds could be envisioned by using the 1-fluoroethene anion for the introduction of the 2-fluoro-1-olefin; this method, in contrast to others currently available,[3] would be applicable to the synthesis of labile fluoro olefins and unsaturated fluoro olefins that could react with ozone. However, to our knowledge neither the 1-fluoroethene anion nor a synthetic equivalent have been reported.

Our impetus for obtaining a synthetic equivalent for the 1-fluoroethene anion was for the preparation of 2'-deoxy-5-(α-fluorovinyl)uridine (20). We envisioned that 20 would be transformed by the action of kinases to the corresponding monophosphate (1), which could be a substrate for thymidylate synthetase and inactivate the enzyme via the mechanism outlined in Scheme 1.[4]

Scheme 1. Proposed Mechanism for Inhibition of Thymidylate Synthase by 1.



Herein, we describe the first synthetic equivalent for the 1-fluoroethene anion (i.e. 10) and its use in the synthesis of 2-fluoro-1-olefins, including the target nucleoside 20. A stereospecific method to (E) and (Z) (1-fluorovinyl)stannanes (6) has been reported by a radical catalyzed stannylation of 2,2-disubstituted fluorovinyl sulfones (5).[5,6] However, attempts to prepare the parent ethene analog (6, R=R'=H), a synthetic equivalent for the 1-fluoroethene anion 11, by the addition of a tributyltin radical to 1-fluoro-1-phenylsulfonylethene

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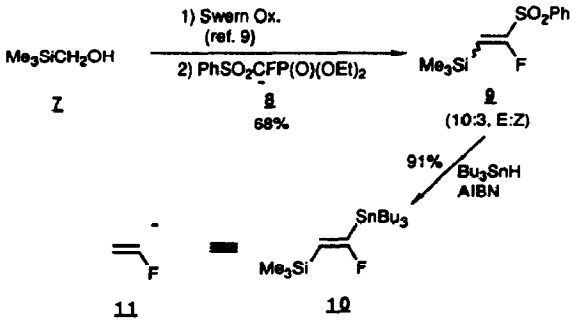
(5, R=R'=H)[7] gave phenyl vinyl sulfone as the only isolated product. To avoid this reaction pathway, a trimethylsilyl group was added at the 2-position of 1-fluoro-1-phenylsulfonylethene to stabilize an adjacent radical;[8] it was envisioned that the trimethylsilyl group could be removed in the last step of the synthesis of 2-fluoro-1-olefins.

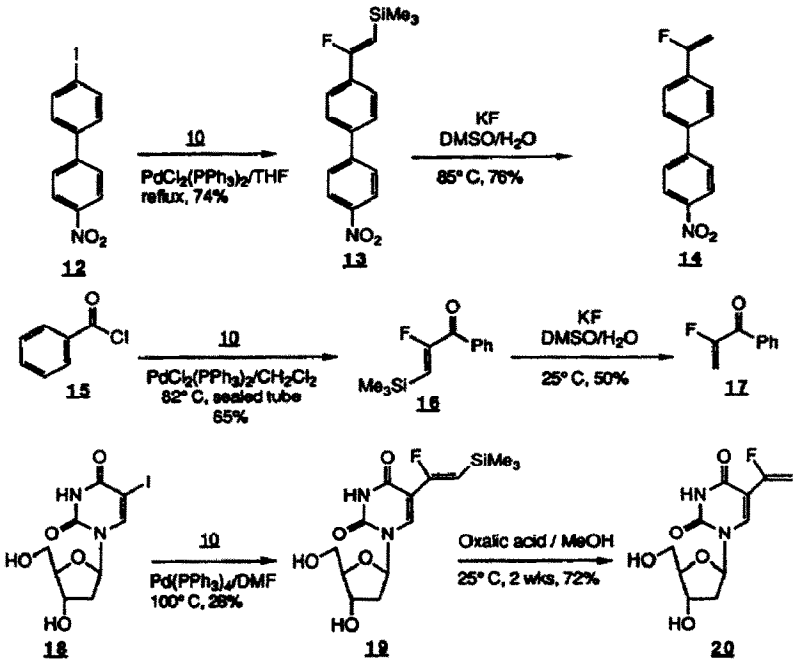
Oxidation of (trimethylsilyl)methanol (7) to the aldehyde by the procedure of Ireland and Norbeck[9] and reaction with the *in situ* generated anion of diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate (8)[10] provided a 10:3 E/Z mixture of 2-trimethylsilyl-1-fluoro-1-(phenylsulfonyl)ethene (9) in 68% yield.[11,12] Treatment of 9 with 2 equivalents of tributyltin hydride and a catalytic amount of AIBN gave the title compound (10) in 91% yield exclusively as the E isomer (Scheme 2).[13,14]

Scheme 2. Preparation of 10
A Synthetic Equivalent for the 1-Fluoroethene Anion.



Palladium catalyzed coupling of 4-iodo-4'-nitrobiphenyl (12) or benzoyl chloride with 10 gave the (Z)1-trimethylsilyl-2-fluoro-1-olefins 13 and 16, respectively, in good yields. (Scheme 3) The trimethylsilyl group was removed from 13 and 16, with aqueous potassium fluoride in DMSO,[15] to provide the 2-fluoro-1-olefins 14 and 17, respectively, in fair to good yields. For the synthesis of the fluoro olefin nucleoside 20, 5-iodo-2'-deoxyuridine (18) was treated with one equivalent of 10 and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in DMF at 100°C for 4 h under argon to give the trimethylsilyl protected fluoro olefin 19. Removal of the vinyl trimethylsilyl group with KF in DMSO/H_2O gave 5-acetyl-2'-deoxyuridine.[16] The undesired and unexpected conversion of the fluoro olefin to a methyl ketone was avoided by removing the trimethylsilyl group with oxalic acid in methanol at room temperature.[17]

Scheme 3. Synthesis of 2-Fluoro-1-olefins.



An illustrative example is as follows:

A mixture of 4-iodo-4'-nitrobiphenyl (12, 325 mg, 1.0 mmol), synthon 10 [13] (430 mg, 1.1 mmol) and bis(triphenylphosphine)palladium(II) chloride in freshly distilled anhydrous THF (15 ml) was heated at reflux for 20 h under a nitrogen atmosphere. The reaction was cooled to room temperature, silica gel (3 g) was added and the mixture was concentrated to a powder. Purification (flash chromotography, silica gel, 1/120 EtOAc/hexane) gave 232 mg (74%) 13, mp 119-121°C (hexane); ^{1}H NMR ($CDCl_3$) δ 0.2 4 (s,9), 5.48 (d,1,J=62Hz), 7.42-8.31 (m,8); ^{19}F NMR ($CDCl_3$) δ -94.7 (d,J=62Hz); MS(EI) m/z 315(M^+). Anal. Calcd for $C_{17}H_{18}FNO_2Si$: C, 64.73; H, 5.75; N, 4.44. Found: C, 64.68; H, 5.83; N, 4.40.

A mixture of 13 (156 mg, 0.49 mmol), KF (800 mg, 13.86 mmol) in DMSO (5 mL) containing 6 drops H_2O was heated at 80°C for 17 h. The reaction was partitioned between EtOAc/H_2O. The EtOAc layer was dried ($MgSO_4$) and concentrated. Purification (flash chromotography, silica gel, 1% EtOAc/hexane) provided 91 mg (76%) 14, mp 142-143°C (hexane); ^{1}H NMR ($CDCl_3$) δ 4.93 (d,1,J=6, 17.7 Hz), 5.12 (dd,1,J=4, 46 Hz), 7.58-8.36 (m,8); ^{19}F NMR ($CDCl_3$) δ -108.7 (dd,J=18,49 Hz); MS (EI) m/z 243 (M^+). Anal. Calcd for $C_{14}H_{10}FNO_2$: C, 69.13; H, 4.14; N, 5.76. Found: C, 69.06; H, 4.12; N, 5.58.

In summary, a new method for the preparation of 2-fluoro-1-olefins from a synthetic equivalent of the 1-fluoroethene anion (10) was developed. The biological activity of 20 will be reported in due course.

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3. See footnote (3) of reference (1) for other synthetic routes to 2-fluoro-1-olefins.
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11. All new compounds gave spectral data consistent with their assigned structure and satisfactory HRMS or elemental analysis.
12. Preparation of 9: To a solution of 18.45 g (106 mmol) fluoromethylphenyl sulfone (ref.10) in 400 ml of THF at -78°C under a nitrogen atmosphere was added 191 ml of a 1.0 M solution of LDA followed by 15.3 ml (106 mmol) of diethyl chlorophosphate and the mixture stirred at -78°C for 1.5 h to provide the fluorosulfone Wittig 8. In a separate round bottomed flask, a solution of 13.9 ml (159 mmol) oxalyl chloride in 500 ml of dichloromethane was cooled to -78°C under a nitrogen atmosphere and treated with 12.8 ml (180 mmol) of dimethyl sulfoxide in 250 ml of dichloromethane over 20 min. The mixture was stirred for an additional 10 min and to this solution was added 13.9 ml (110 mmol) of trimethylsilylmethanol in 150 ml of dichloromethane and the mixture stirred for 15 min at -78°C. Then 55 ml (392 mmol) of triethylamine was added and the mixture stirred at -78°C for 20 min. To this solution was added the solution of 8 via cannula and the mixture stirred at -78°C for 1 h, allowed to warm to ambient temperature and stirred one additional hour. The reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated and the aqueous phase extracted three times with chloroform and the combined organic phases dried over magnesium sulfate. The crude product was purified by flash chromatography on silica gel (1:5 ethyl acetate/hexanes) affording 21.2 g (77%) of fluorovinyl sulfone 9 as a 10:3 mixture of E/Z isomers.
13. Preparation of 10: To 21.2 g (82 mmol) of fluorovinyl sulfone 9 in 400 ml of toluene under a nitrogen atmosphere was added 670 mg (4.1 mmol) AIBN and 48.5 ml (180 mmol) of tri-n-butyltin hydride. The mixture was refluxed for 24 h, cooled, and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (hexanes) affording 30.4 g (91%) of (fluorovinyl)stannane 10.
14. The conversion of 2,2-disubstituted-1-fluoro-1-(phenylsulfonyl) ethenes to (fluorovinyl)stannanes proceeds with retention of configuration (ref. 5); however, 2-monosubstituted derivatives equilibrate during the free radical reaction (ref. 6 and Matthews, D.P.; Huber, E.W.; McCarthy, J.R., in preparation).
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