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A NEW SYNTHESIS OF 2-FLUORO-1-OLEFINS

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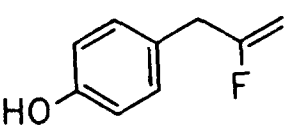
Abstract: The first examples of the addition of PhSeF to olefins to yield β-fluoro phenylselenides (2) are reported. β-Fluoro phenylselenides (2) obtained from terminal olefins were converted to the title vinyl fluorides 3 on treatment with ozone, whereas, 2 obtained from internal and cyclic olefins formed allyl fluorides. This method provides an entry to previously unreported 2-benzyl-2-fluoro-1-olefins (e.g. 3i).

Synthetic methods to fluoroorganics are receiving considerable attention because of the importance of these compounds as medicinal agents and as probes for understanding metabolic and enzymatic processes.[1] Several convenient methods for the preparation of 1-fluoro-1-olefins (terminal vinyl fluorides) have been developed recently.[2] However, synthetic routes to 2-fluoro-1-olefins often do not proceed in good yield.[3] The preferred method to 2-fluoro-1-olefins is a two step sequence of HF/pyridine/N-bromosuccinimide followed by treatment with a strong base.[3a] 2-Fluoro-1-olefins must be separated from 1-fluoro-1-olefin and acetylenic products.

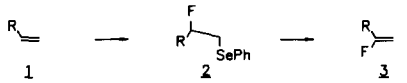
We reasoned that a more promising approach to the title compounds (3) might be via β-fluoro selenoethers (2). Recently, two reports on the formation of β-fluoro thioethers by the addition of alkylsulfenyl fluorides to olefins have appeared[4]. Nash and Gamill[5] obtained β-fluoro thioethers and β-fluoro selenoethers of khellin (a furochromone natural product) via nucleophilic displacement of a benzylic bromo group with a thio or seleno nucleophile. Syn-elimination of the corresponding sulfoxide afforded a 4% yield of 2-fluorokhellin. Similarly, oxidation of the 2-fluoro selenoether of khellin (MCPBA or H_2O_2/HOAc) led to 2% 2-fluorokhellin (the authors proposed that the poor yields of vinyl fluoride were due to an unfavorable electronic influence of fluorine on the syn-elimination process). We report the first examples of the trans addition of phenylselenyl fluoride to olefins to provide β-fluoro phenylselenides (2) and in the case of terminal olefins, the conversion of 2 to 2-fluoro-1-olefins (3) in good yields. This method was applied to the synthesis of 2-benzyl-2-fluoro-1-olefin 3i, a compound of interest as a potential mechanism-based inhibitor of dopamine β-hydroxylase[6] (see recent work of Villafranca and co-workers[7]).

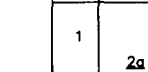
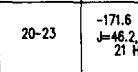
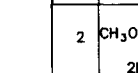
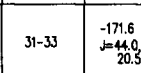
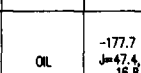
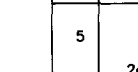
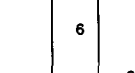
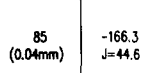
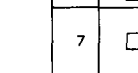
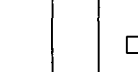
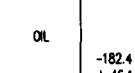
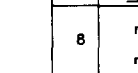
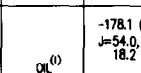
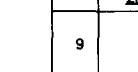
Table 1 lists examples of the synthesis of β-fluoro phenylselenides (2a-2h). The reaction is generally regioselective and stereospecific. Predominant Markovnikov addition of PhSeF to olefins was observed with the exception of entry 4, where the olefin has a heteroatom in the β-position. In this case, a 1 to 1 mixture of the two isomers was observed and the desired β-fluoro phenylselenide (2d) was easily isolated by flash chromatography. To determine the stereochemistry of PhSeF addition to olefins, cyclohexene was chosen as a model compound (see entry 6). The reaction proceeded stereospecifically by anti-addition of PhSeF to provide 2f in 92% yield.[8,9] Hindered olefins (e.g. trans-stilbene) and electron deficient olefins (see entry 9) were unreactive. Applying the ozonolysis procedure of Reich and co-workers[10] to β-fluoro phenylselenides 2a-2d, followed by refluxing the resulting fluoroselenoxides in carbon



3i

Table 1. PREPARATION OF β-FLUORO PHENYLSELENIDES (2) AND CONVERSION TO 2-FLUORO-1-OLEFINS (3)



ENTRY	β-FLUORO PHENYLSELENIDE (2) (YIELD) [a]	mp,°C or bp,°C(mm) [b]	^{19}F NMR (vs. $CFCl_3$)	2-FLUORO-1-ALKENE(3) (YIELD) [a]	mp,°C or bp,°C(mm) [b]	^{19}F NMR (vs. $CFCl_3$) (282 MHz)
1	 [c] 2a (53%)	20-23	-171.6 (dtt) J=46.2, 27, 21 Hz	 3a (83%)	50-60 (0.05mm)	-95.0 (ddt) J=49.4, 16, 16 Hz
2	 2b (64%)	31-33	-171.6 (dtt) J=44.0, 25.4, 20.5 Hz	 3b (66%)	77-78	-95.1 (ddt) J=49.1, 15.8, 15.2 Hz
3	$CH_3(CH_2)_9CHCH_2SePh$ 2c (94%)	37-38	-173.3 (m)	$CH_3(CH_2)_9C=CH_2$ (d) 3c (67%)	85-89 (10mm)	-94.3 (ddt) J=50.3, 16.6, 16.6 Hz
4	 (e) 2d (31%)	OIL	-177.7 (dtt) J=47.4, 21.8, 16.8 Hz	 3d (67%)	OIL	-106.8 (dddd) J=48.2, 16.6, 10.2, 10.4 Hz
5	 2e (13%)	OIL	-111.0 (dd) J=54.9, 18 Hz	(f)	———	———
6	 2f (92%)	85 (0.04mm)	-166.3 (brd) J=44.6 Hz	 (g) 4f (100%)	OIL	-166.0 (brd) [h] J=49.5 Hz
7	 from trans-1e +  from cis-1e 2g (2.6:1) [i] (71%)	OIL	-178.6 (m) -182.4 (dtt) J=46.1, 28.7, 16.7 Hz	 4g (98%)	OIL [j]	-167.8 (brd) J=43.5 Hz
8	 2h (3.0:1) [k] (67%)	OIL [l]	-178.1 (ddt) J=54.0, 20.0, 18.2 Hz -179.5 (dddd) J=51.0, 31.5, 17.0, 16.0 Hz	 4h (100%)	OIL [j]	-171.0 (m)
9	 1i No product after 18 hrs	———	———	———	———	———

[a]Flouroselenylation reactions were allowed to proceed 18 h. All β-fluorophenylselenides (2) and 2-fluoro-1-olefins (3) are fully supported by ^{1}H NMR, ^{19}F NMR, MS, elemental analysis and/or HRMS. [b]Kugelrohr distillation. [c]Gas chromatographic analysis of reaction mixture showed a 6.3 to 1 mixture of 2a to 1-fluoro-2-phenylselenide. [d]Reference 3e. [e]The 1-fluoro-2- phenylselenide also isolated in 44% yield; ^{19}F NMR (vs. $CFCl_3$)-212.4 (dt). [f]Compound 2e was unstable to ozonolysis reaction. [g]Quantitative conversion by ^{1}H and ^{19}F NMR. See reference 11. [h]Identical to literature ^{19}F NMR. See reference 11. [i]Cyclododecene was a 2 to 1 mixture of trans to cis olefin by ^{13}C NMR. [j]Structure established by ^{1}H NMR, ^{19}F NMR. Unstable to Kugelrohr distillation/flash chromatography. [k]7-Tetradecene was a 3 to 1 mixture of trans to cis isomers by ^{13}C NMR. [l]Observed loss of PhSeF on flash chromatography and formation of starting olefin. Crude 2h after filtration through Celite was evaporated to an oil, dissolved in CCl_4 and treated with O_3, destroying any unreacted starting olefin.

tetrachloride and diisopropylamine provided good yields of the 2-fluoro-1-olefins (3a-3d); other methods for this transformation (MCPBA or H_2O_2/HOAc) gave poor yields of 3. β-Fluoro phenylselenides obtained from cyclic olefins (2f and 2g), as well as internal olefins (2h), formed allyl fluorides exclusively on treatment with ozone.[11] This is in contrast to β-chloro phenylselenides which were reported to give a mixture of allyl chlorides and vinyl chlorides.[12] A direct comparison was made for entry 6 in Table 1, where the trans-β-chloro phenylselenide of cyclohexane was reported to give a 1 to 1 mixture of 1-chlorocyclohex-1-ene and 3-chlorocyclohex-1-ene[12a]. The contrast between β-chloro and β-fluoro phenylselenides is of interest[13] and presents a clear case for further theoretical study of the effect of an α-fluorine on the C-H bond.[14,15]

The synthesis of 3a is outlined below:

To a dry 250 mL flask with septum and argon bubbler was added finely ground AgF (6.30 g, 50 mmol, glove bag), dry CH_3CN (100 mL), 4-allylanisole (2.96 g, 20 mmol) and phenylselenenyl chloride (4.6 g, 24 mmol) (dissolved in 25 mL CH_3CN) via syringe. The reaction was stirred at room temperature and the formation of β-fluoro phenylselenide from olefin was monitored by gas chromatography. After 18 h, the reaction was filtered through a Celite pad and treated with flash silica gel (ca. 15 mL). The mixture was evaporated to a powder (<30°C) and the desired product (2a) was separated from a small amount of 1-fluoro-2-phenylselenide by flash chromatography (10% ether in hexane) and was isolated as a white crystalline solid (3.39 g, 53%), mp 20-23°C . ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90-3.19 (m, 4), 3.79 (s, 3), 4.80 (dm, 1, J = 47.6 Hz), 6.83 (d, 2, J = 8.7 Hz), 7.10 (d, 2, J = 8.7 Hz), 7.25 (m, 3), 7.50 (m, 2). ^{19}F NMR ($CDCl_3$) δ (vs. $CFCl_3$, 282 MHz) - 171.6 (dtt, J = 46.2, 27, 21 Hz); MS (CI/CH_4) m/z 325 (MH^+ for ^{80}Se). Anal. Calcd for $C_{16}H_{17}FOSe$: C, 59.44; H, 5.30. Found: C, 59.50; H, 5.29.

A solution of 2a (1.0 g, 3 mmol) in CCl_4 (100 mL) was cooled to -20°C and ozone was bubbled through the solution until a light blue color persisted. Diisopropylamine (0.6 g, 6 mmol) was added and the solution was heated at reflux for 16 h, washed with ice cold dilute HCl (2 x 50 mL), aq $NaHCO_3$ (50 mL) and dried ($MgSO_4$). The solution was evaporated to an oil and purified by flash chromatography (hexane) to provide 3a as a colorless oil (415 mg, 83%). Kugelrohr distillation of a small sample at 50-60°C (0.05 mm) provided analytically pure 3a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (d, 2, J = 14.9 Hz), 3.80 (s, 3), 4.21 (ddt, 1, J = 49.4, 2.8, 0.9 Hz), 4.58 (dd, 1, J= 16.8, 2.7 Hz), 6.86 (d, 2, J = 8.7 Hz), 7.17 (d, 2, J = 8.7 Hz); ^{19}F NMR ($CDCl_3$) δ (vs. $CFCl_3$, 282 MHz) -95.0 (ddt, J = 49.1, 15.8, 15.2 Hz); MS (CI/CH_4) m/z 167 (MH^+). Anal. Calcd. for $C_{10}H_{11}FO$: C, 72.27; H, 6.67. Found: C, 72.33; H, 6.78.

Demethylation of 3a with trimethylsilyl iodide in CH_2Cl_2 and workup with rapidly stirring ice cold aq $NaHSO_3$ and $NaHCO_3$ gave 3-(4-hydroxyphenyl)-2-fluoro-1-propene (3i) and variable amounts of the HI addition product. Pure 3i was obtained by deprotection of benzyl ether 3b with saturated methanolic HCl for 1 h at room temperature followed by a standard extractive workup for isolation of phenols to provide 3i[16] in 89% yield as an oil. Compound 3i demonstrates time dependent enzyme kinetics consistent with a mechanism-based inhibitor of dopamine β-hydroxylase[17] and is the first reported vinyl fluoride mechanism-based inhibitor of this enzyme. The enzyme inhibition data for 3i will be reported elsewhere. In summary, a new method for the synthesis of 2-fluoro-1-olefins from terminal olefins is now available, which was applied to the synthesis of an inhibitor of dopamine β-hydroxylase. This procedure will be the method of choice in many cases such as 2-benzyl-2-fluoro-1-olefins.

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6. See Bargar, T.M.; Broersma, R.J.; Creemer, L.C.; McCarthy, J.R.; Hornsperger, J.-M.; Atwood, P.V.; Jung, M.J. J. Am. Chem. Soc. 1988, 110, 2975, and references cited therein.
7. The corresponding 2-chloro-and 2-bromo-1-olefins were prepared by Villafranca, et al. and demonstrated time-dependent inactivation of DBH: see Rajashekhar, B.; Fitzpatrick, P.F.; Colombo, G.; Villafranca, J.J. J. Biol. Chem. 1984, 259, 6925.
8. ^{1}H NMR of 2f ($CDCl_3$, 300 MHz) δ 4.45 (dddd, 1, J = 44.6, 8.5, 8.5, 4.0 Hz), which is consistent with trans addition of PhSeF to cyclohexene.
9. trans Addition of PhSeF across cyclododecene (entry 7) and 7-tetradecene (entry 8) provided β-fluoro phenylselenides 2g and 2h as a mixture of diastereomers in the same ratio as that of (E) to (Z) geometric isomers in the starting olefins. Ratios were determined by ^{13}C NMR for starting olefins and ^{19}F NMR for 2g and 2h (see Table 1).
10. Reich, H.J.; Shah, S.K. J. Am. Chem. Soc., 1975, 97, 3250; See also Clark, R.D.; Heathcock, C.H. J. Org. Chem. 1976, 41, 1396.
11. For entry 6, authentic 3-fluorocyclohexene was prepared by the treatment of 2-cyclohexen-1-ol with diethylaminosulfur trifluoride (DAST): ^{19}F NMR δ (vs. $CFCl_3$ 282 MHz) - 166.0 (br d, J = 49.5) which is identical with the reported ^{19}F NMR by Hudlicky, M. J. Fluorine. Chem. 1986, 32, 441, who also reported ^{19}F NMR for 1-fluorocyclohexene δ - 100.5 (br s).
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13. The contrast in reactivity for the acyclic cases may, in part, be explained by the 'gauche effect', (ref. 14) where fluorine would stabilize the gauche conformation between fluorine and the phenylselenoxide. However, the cyclohexyl case indicates that electronic effects of the fluorine may play a major role in the formation of allyl fluorides (ref. 15).
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15. Sharpless has observed a similar effect with selenoxide eliminations preferentially occurring away from an oxygen substituent: Sharpless, K.B; Lauer, R.F. J. Am. Chem. Soc. 1973, 95, 2697; see also Liotta, D.; Zimu, G.; Saindane, M. J. Org. Chem. 1982, 47, 1258.
16. Compound 3i: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (d, 2, J = 15 Hz), 4.22 (ddt, 1, J = 46.5, 2.1, 0.6 Hz), 4.61 (dd, 1, J = 16.8, 2.7 Hz), 6.79 (d, 2, J = 8.4 Hz), 7.12 (d, 2, J = 8.7 Hz); ^{19}F NMR ($CDCl_3$) δ (vs. $CFCl_3$, 282 MHz) - 95.05 (ddt, J = 64.4, 49.1, 15.2 Hz); MS (CI/CH_4) m/z 153 (MH^+). HRMS Calcd for C_9H_9FO: 152.0637. Found: 152.0636.
17. Broersma, R.J., unpublished results.

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