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A NEW ROUTE TO VINYL FLUORIDES

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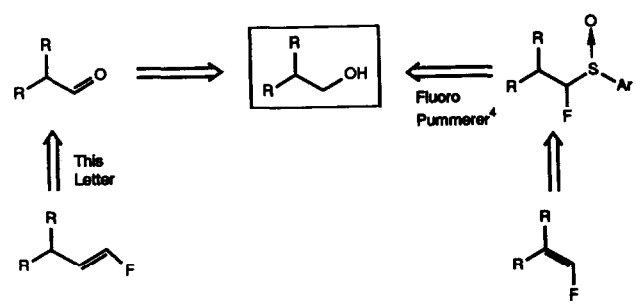
Abstract: *The carbanion of diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate (7), generated in situ from fluoromethyl phenyl sulfone (3) undergoes the Horner-Wittig reaction with aldehydes and ketones to yield α-fluoro-α,β-unsaturated sulfones (8). Reductive removal of the phenylsulfonyl group provides a facile two-step route to vinyl fluorides from 3, where the fluorine source is either KF or DAST.*

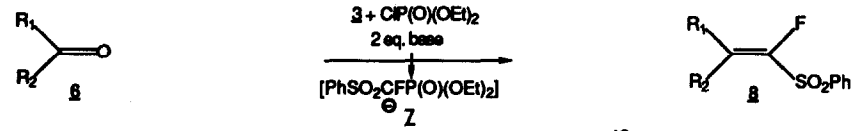
Interest in new methods to vinyl fluorides has intensified,[1,2] in part, because of the presence of this group in a number of enzyme inhibitors.[3] Recently, we reported a method to vinyl fluorides[4] utilizing a fluoro Pummerer reaction and applied it to the synthesis of 4',5'-vinyl fluoride nucleosides.[3c] The reaction can be viewed as a formal dehydration of an alcohol (via conversion to an aryl sulfoxide) after introduction of fluorine (see Scheme 1). A convenient route to vinyl fluorides from alcohols (via aldehydes and ketones) by the formal addition of a fluoromethylene group was also needed. Methods currently available for this transformation that rely on Wittig-type reagents have met with limited success.[1d,5,6] Fluoromethyl phenyl sulfone (3)[7] was demonstrated to be useful for the conversion of aromatic aldehydes to vinyl fluorides via α-fluoro-α,β-unsaturated sulfones (8). However, the reaction was not general since acetophenone and other aldehydes and ketones containing α-hydrogens gave allyl fluoro sulfones. Recently, Finch and coworkers[1a] utilized fluoromethyl N-methyl phenylsulfoximine, a novel reagent obtained from 3, for the synthesis of vinyl fluorides. Of interest to us for a shorter and more convenient route to carry out this transformation was diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate (5). This reagent was recently obtained using freshly prepared perchloryl fluoride ($FClO_3$)[8], a compound that should be used with extreme caution.[9]

SCHEME 1.



We report a convenient method for the in situ generation of the carbanion of reagent 5 (i.e., 7, see Table) from fluoromethyl phenyl sulfone (3) and demonstrate its utility in vinyl fluoride preparation by reaction with aldehydes and ketones. Carbanion 7 was generated from fluoromethyl phenyl sulfone (3), diethyl chlorophosphate and two equivalents of either LDA or lithium hexamethyldisilazane (LiHMDS) at -78°C. Carbonyl compounds were added directly to the

Table 1. Synthesis of α-Fluoro-α,β-Unsaturated Sulfones (8).[a]



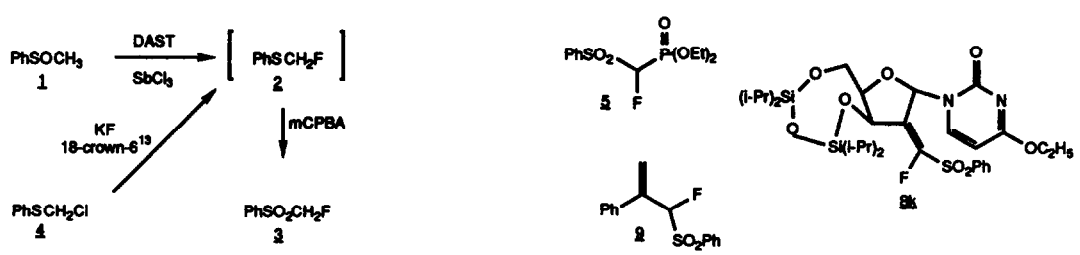
8	E/Z ratio[b]	Yield, %	base	mp, °C	^{19}F NMR (vs. $CFCl_3$, 282 MHz)
8a	1/1	87	LDA	89-91	(E) -116.2(q, J=4.3Hz) (Z) -119.9(q, J=3.4Hz)
8b	-	84	LDA	oil	-122.6(m)
8c	1.3/1	95	LDA	oil	(E) -118.8(q, J=4.5Hz) (Z) -122.6(q, J=3.4Hz)
8d	-	80	LiHMDS	103-04[c]	-117.2(s)
8e	4.4/1	85	LDA	163-65[d]	(E) -199.9(d, J=34Hz)[d]
8f	-	75	LDA	103-04	-123.5(s)
8g	1.9/1[e]	44	LiHMDS	oil	(E) -122.3(d, J=32Hz) (Z) -113.7(d, J=21Hz)
8h	3/1[f]	60	LDA	131-32	(E) -111.0(s)[g] (Z) -117.8(s)
8i	1/9.4	90	LiHMDS	foam	(E) -114.9(s)[g] (Z) -118.8(s)
8j	2.7/1[h]	71	LDA	oil	(E) -129.4(d, J=32Hz) (Z) -117.2(d, J=23Hz)

[a] All new compounds gave spectral data consistent with the assigned structure and with the exception of the (Z)-isomer of 8g, gave satisfactory elemental analyses. The reaction conditions were the same as presented for 8e, with the exception of 8g, 8h and 8i (see text). [b] E/Z ratios were determined by GC on reaction mixtures, except where noted. [c] Lit.[6] mp 94-95°C. [d] Crystallized from hexane as pure (E)-isomer; Lit.[7] mp 157-58°C. [e] The (E)- and (Z)-isomers were separated by flash chromatography; cyclohexane/EtOAc(3/1). [f] Crystalline 8h. [g] Assignments were made by $^3J_{CF}$ coupling constants. [h] Ratio determined by ^{19}F NMR on isolated material.

solution of 7, which was allowed to warm to ambient temperature, and the desired α-fluoro-α,β-unsaturated sulfones (8) were isolated in good to excellent yields (see Table 1). The generality of the method is demonstrated by the formation of nucleosides 8h and 8i. Reactions with base-sensitive compounds had to be carefully monitored. Thus, optimum conditions for the synthesis of 8h required addition of the ketone to carbanion 7 at 0°C and quenching the reaction with aqueous ammonium chloride after 90 minutes at 0°C. For the synthesis of 8i, care had to be taken to avoid the presence of excess base since a slight excess of LDA led to the isolation of the α-lyxo nucleoside 8k in 23% yield.[10] The carbohydrate 8g was also base sensitive; the reaction was kept at -78°C for 30 minutes after addition of the aldehyde, warmed to -35°C for 4 minutes and quenched with aqueous ammonium chloride. It should be noted that acetophenone was converted to the desired product 8c in 95% yield. This is in contrast to our earlier method[7] for 8c utilizing reagent 3 that gave the allyl fluoro sulfone 9. We have previously shown that α-fluoro-α,β-unsaturated sulfones 8 are converted to vinyl fluorides in high yield with amalgamated aluminum.[7]

The ease of synthesis of fluoromethyl phenyl sulfone (3) on a multigram scale[11] from methyl phenyl sulfoxide in 93% yield is a key point in making this method to vinyl fluorides of general synthetic utility. We found that modification of our original procedure[7] for the synthesis of 3 by the addition of a catalytic amount of Robins catalyst, $SbCl_3$,[12] to the solution of DAST and phenyl methyl sulfoxide followed by the addition of MCPBA to the intermediate fluoromethyl phenyl sulfide (2) (without isolation) increased the yield substantially. It should be noted that Wemple[13] has reported the conversion of chloromethyl phenyl sulfide (4) to fluoromethyl phenyl sulfide (2) with KF and 18-crown-6. Thus, the methods available for the preparation of 3 provide readily available sources of fluorine for the preparation of vinyl fluorides.

SCHEME 2.



The procedure for the synthesis of vinyl fluorides is illustrated with the synthesis of β-fluoro-4-chlorostyrene (10e): A solution of LDA (3.86 mmol) (prepared from diisopropylamine and 1.6 M BuLi in hexane) in THF (15 mL) at -78°C was added to a solution of fluoromethyl phenyl sulfone (3)[11] (375 mg, 2.15 mmol) in dry THF cooled to -78°C. Diethyl chlorophosphate (freshly distilled) (371 mg, 0.31 mL, 2.15 mmol) was added and the reaction was stirred at -78°C for 60 min. A solution of 4-chlorobenzaldehyde (201 mg, 1.43 mmol) in THF (4 mL) was added, and the solution was warmed to ambient temperature and stirred for 16 hrs. The reaction was poured into ice cold aq. NH_4Cl and extracted with ethyl acetate (3x50 mL). The combined organic layers were dried ($MgSO_4$), evaporated in vacuo and filtered through a flash silica gel column (EtOAc:hexane 1:5) to provide 360 mg (85%) of crystalline 8e as a 86:14 mixture (determined by GC) of E to Z geometric isomers. Recrystallization from EtOH gave 250 mg of pure E isomer, mp 163-165°C (Lit[7] mp 157-158°C); MS (EI, 70 ev) 296 (M^+); ^{19}F NMR ($CDCl_3$,

282 MHz, from $CFCl_3$) -199.9 (d, J=34 Hz); Anal. Calcd for $C_{14}H_{10}ClFSO_2$: C, 56.66; H, 3.37. Found: C, 56.67; H, 3.32. Reductive cleavage of the phenylsulfonyl group was accomplished by treating a solution of 8e (592 mg, 2 mmol) in 9:1 THF-H_2O (100 mL) under nitrogen with freshly prepared aluminum amalgam [from 1 gm (0.04 gm atom) of Al foil and 2% ag $HgCl_2$ by the procedure of Corey and Chaykovsky[14]]. The mixture was heated at reflux for 2 hr, filtered and the filtrate evaporated to remove most of the THF. The solution was extracted with ether (2x25 mL) and dried ($MgSO_4$). Purification by flash chromatography on silica gel (hexane) gave 282 mg (90%) of β-fluoro-4-chlorostyrene (10e) as a 1:1 mixture of E to Z isomers, bp 75-80°C (0.05 mm) (lit.[7] bp 75-80°C (0.05 mm).

In summary, a general and facile method to fluoro vinyl sulfones (8) from aldehydes and ketones using the in situ generated reagent 7 in a Horner-Wittig reaction is reported. This provides a convenient route to vinyl fluorides via our previously reported method for the conversion of 8 to vinyl fluorides with amalgamated aluminum.[7]

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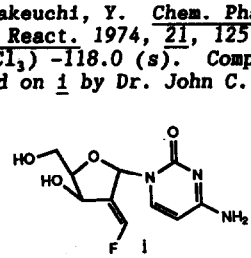

11. Preparation of 3: A mixture of methyl phenyl sulfoxide (22.5 g, 0.16 M), $CHCl_3$ (100 mL), DAST (34.3 g, 0.213 M) and $SbCl_3$ (ca. 440 mg, 2 mM) in a 1 L flask with a reflux condenser was stirred and cooled with an ambient temperature water bath under argon. After 3-5 hr a mild exotherm was observed and the reaction was poured into cold sat. aq. $NaHCO_3$ (600 mL, with 10 g NaOH), extracted with $CHCl_3$ and dried (K_2CO_3). Addition of 85% of MCPBA portionwise (90 g) over 30 min, extractive workup with aq. $NaHSO_3$ and aq. $NaHCO_3$ followed by evaporation of the $CHCl_3$ gave 27.9 g of white crystalline solid after drying under high vacuum. Recrystallization from hexane (200 mL, 2 phase system) gave pure 3 as white crystals (26.4 g, 94%), mp 53-54°C. (See ref. 7 for previous synthesis).
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