A Novel and Efficient Synthesis of Fluoromethyl Phenyl Sulphone and Its Use as a Fluoromethyl Wittig Equivalent[1]

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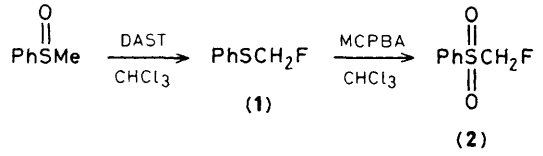
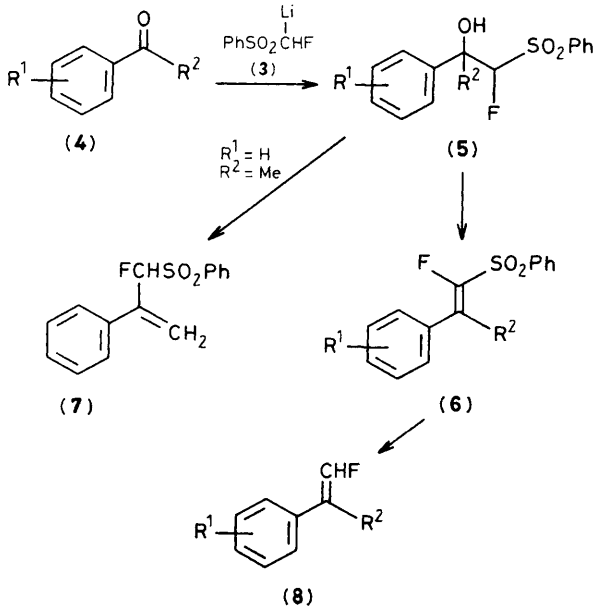
A new synthesis of fluoromethyl phenyl sulphone (**2**) and the reaction of its conjugate base (**3**) with carbonyl compounds provides β-fluoro-alcohols (**5**), which are utilized to prepare terminal vinyl fluorides (**8**) *via* α-fluoro-α,β-unsaturated sulphones (**6**).

Convenient syntheses of vinyl fluorides[2] are of particular interest because of their potential to act as irreversible enzyme inhibitors.[3] We report herein a new route to vinyl fluorides which utilizes the reagent fluoromethyl phenyl sulphone (**2**). In addition, we report a new synthesis of (**2**) which is far more efficient than the multi-step process in the literature.[4]

Using our recently described procedure for the conversion of sulphoxides into α-fluoro-sulphides,[1] we prepared fluoromethyl phenyl sulphide (**1**) from methyl phenyl sulphoxide in 85% yield. Oxidation of (**1**) with *m*-chloroperbenzoic acid (MCPBA; 2 equiv.) afforded the sulphone (**2**) in 93% yield (Scheme 1). Lithiofluoromethyl phenyl sulphone (**3**) [prepared by dropwise addition of 1 equiv. of Bu^{n}Li to a solution of (**2**) in tetrahydrofuran (THF) at −78 °C], when treated with



Scheme 1. DAST = Et_2NSF_3



Scheme 2

carbonyl compounds (**4**), gave β-fluoro-alcohols (**5**) in high yields (Scheme 2). In contrast, carbanions derived from chloromethyl and bromomethyl aryl sulphones are known to condense with aldehydes and ketones to give oxiranes.[5] The high-yield synthesis of the alcohols (**5**) provided an entry to vinyl fluorides, since (**5**) were transformed to *E*-α-fluoro-α,β-unsaturated sulphones (**6a—d**) in overall yields of 67—92% on treatment with methanesulphonyl chloride (1.1 equiv.).

The assignment of the stereochemistry for (**6a—d**) is derived from the ^{1}H n.m.r. data.[6] The exclusive formation of the *E*-isomers (**6a—d**) during the elimination reaction can be rationalized from the steric repulsion between the bulky aryl and phenylsulphonyl groups apparent from Newman projections of the methanesulphonates of (**5**).

Reductive removal of the phenylsulphonyl group from the vinyl sulphones (**6a**), (**6b**), and (**6e**) was readily achieved by treatment with aluminium amalgam (THF–H_2O at reflux for 1—3 h).[7] The vinyl fluorides (**8a**),[8] (**8b**),[9] and (**8e**)[10] were obtained in *ca.* 90% yield. ^{1}H N.m.r. analysis of (**8a**) and (**8b**) showed them to be 1:1 mixtures of *E*- and *Z*-isomers. Reductive removal of the sulphonyl group in the presence of a vinyl fluoride functionality has not previously been described. It should be noted that the use of the Wittig reaction *per se* to prepare vinyl fluorides has been reported to be very sensitive to reaction conditions and requires extremely dry solvents to obtain satisfactory and reproducible yields.[11]

In the case of the alcohol (**5e**; R^1 = H, R^2 = Ph), the desired dehydration to give (**6e**) was readily accomplished in 85% orthophosphoric acid (100—165 °C; 1 h),[12] while the mesylation–elimination sequence proved less satisfactory. Interestingly, the alcohol (**5f**) derived from acetophenone, when treated with methanesulphonyl chloride and triethylamine gave the β,γ-unsaturated sulphone (**7**) exclusively, and not the α,β-isomer (**6f**), as shown by ^{1}H n.m.r. spectroscopy. The greater thermodynamic stability of the β,γ-unsaturated isomers of similar sulphones has been demonstrated by O'Conner[13] and Posner.[14]

In conclusion, fluoromethyl phenyl sulphone is a useful fluoromethyl Wittig equivalent in the homologation of carbonyl compounds to terminal vinyl fluorides.

Table 1. α,β-Unsaturated sulphones (**6**), β,γ-unsaturated sulphone (**7**), and vinyl fluorides (**8**) obtained using reagent (**2**).

Product	R^1	R^2	% Yield	M.p., *t*/°C	Method[a]
(**6a**)	H	H	67	77.5—78.5	A
(**6b**)	4-Cl	H	80	157—158	A
(**6c**)	3,4-$(OMe)_2$	H	71	118—119	A
(**6d**)	2,3,4,5,6-F_5	H	78	112—113	A
(**6e**)	H	Ph	92	94—95	B
(**6f**)	H	Me	—	—	—
(**7**)	—	—	82	81—82.5	A
(**8a**)	H	H	90	Oil[b]	C
(**8b**)	4-Cl	H	90	Oil[c]	C
(**8e**)	H	Ph	91	Oil[b]	C

[a] Method A: $MeSO_2Cl$ (1.1 equiv.), Et_3N (2.5 equiv.) in CH_2Cl_2. Method B: 85% orthophosphoric acid, 100—165 °C over 1 h. Method C: aluminium amalgam, THF–H_2O at reflux for 3 h. [b] Purified by flash chromatography. [c] B.p. 75—80 °C at 0.05 mmHg (ref. 9, b.p. 77 °C at 0.05 mmHg).

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