

A Novel and Efficient Synthesis of Fluoromethyl Phenyl Sulphone and Its Use as a Fluoromethyl Wittig Equivalent¹

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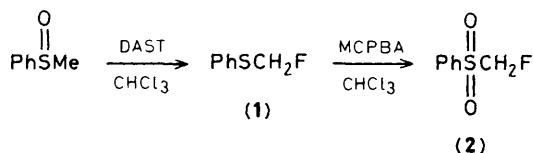
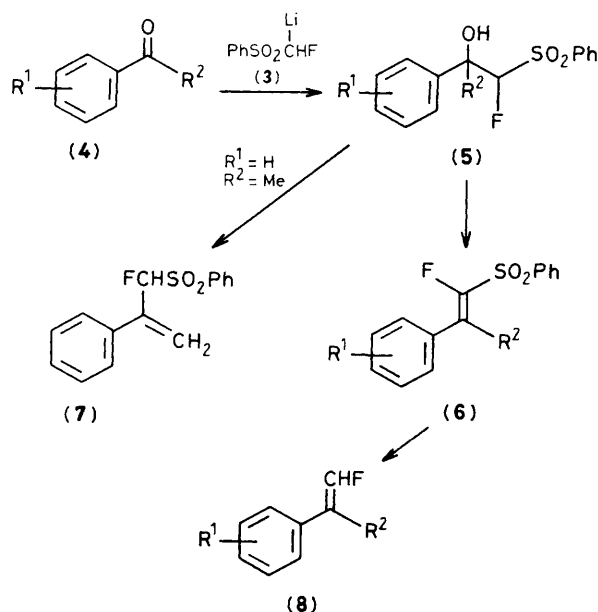
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A new synthesis of fluoromethyl phenyl sulphone (**2**) and the reaction of its conjugate base (**3**) with carbonyl compounds provides β -fluoro-alcohols (**5**), which are utilized to prepare terminal vinyl fluorides (**8**) via α -fluoro- α,β -unsaturated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

Convenient syntheses of vinyl fluorides² 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 BuⁿLi to a solution of (**2**) in tetrahydrofuran (THF) at -78°C], when treated with

Scheme 1. DAST = Et₂NSF₃

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 ¹H 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–H₂O at reflux for 1–3 h).⁷ The vinyl fluorides (8a),⁸ (8b),⁹ and (8e)¹⁰ were obtained in ca. 90% yield. ¹H 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; R¹ = H, R² = Ph), the desired dehydration to give (6e) was readily accomplished in 85%

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: MeSO₂Cl (1.1 equiv.), Et₃N (2.5 equiv.) in CH₂Cl₂. Method B: 85% orthophosphoric acid, 100–165 °C over 1 h. Method C: aluminium amalgam, THF–H₂O 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).

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 ¹H n.m.r. spectroscopy. The greater thermodynamic stability of the β,γ -unsaturated isomers of similar sulphones has been demonstrated by O'Connor¹³ and Posner.¹⁴

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

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References

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