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α-FLUOROMETHYL-N-METHYL-PHENYLSULPHOXIMINE: A NEW FLUOROMETHYLENATION REAGENT

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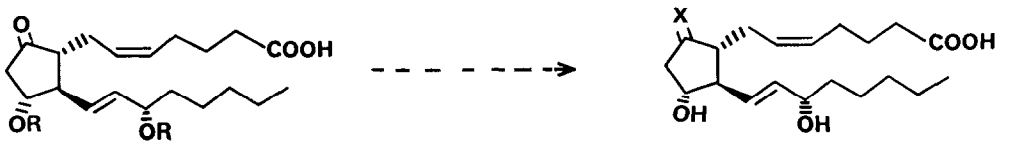
ABSTRACT: Treatment of aldehydes or ketones with the anion derived from α-fluoromethyl-N-methyl-phenylsulphoximine produces adducts which afford fluoro-olefins on reductive elimination.

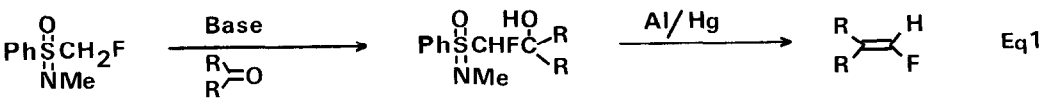
The large number of recent publications[1] describing the introduction of fluorine into bioactive organic molecules testifies to the importance of new and selective methodology in this field. Prostaglandins have not escaped bioisosteric fluorine incorporation and a variety of PGF, PGE and PGI analogues have been synthesised and pharmacologically evaluated[1].

As part of our continuing search for selectively acting prostanoids we were interested in the above approach and also the observation[2] that 9-desoxo-9-methylene PGE_2 (2) is much more stable than its natural counterpart. We reasoned that introduction of the related 9-fluoromethylene moiety (i.e. 3) would not only confer chemical stability but also serve to reinstate a similar dipole moment at C-9 thus ensuring a closer resemblance to natural PGE_2.



(1) R=Si*t*-BuMe$_2$ **PGE_2 X=O ; (2) X=CH_2; (3) X=CHF**

At the outset we decided that the simplest approach to the fluoro-olefin (3) would be via the base-sensitive ketoacid[3] (1), and so a mild fluoromethylenation procedure was required. Inspection of the literature methods[4] available was not encouraging and we argued that since the sulphoximine olefination strategy developed by Johnson[5] had already been successfully applied[2] to an analogue of the ketone (1), the related but novel fluorosulphoximine (4) might prove to be a useful, mild fluoromethylenation reagent (Eq. 1).

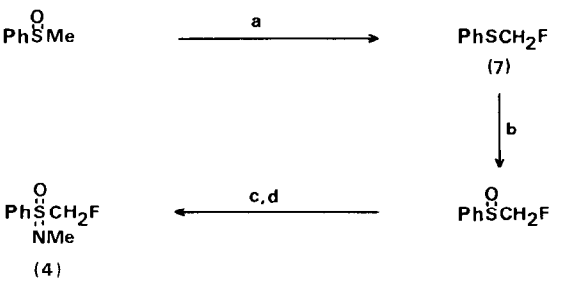


(4) (5) (6) Eq1

Our synthetic route to sulphoximine (4) was based on the recent report by McCarthy[6] who showed that methyl phenyl sulphoxide could be converted into the fluorosulphide[7] (7) on

treatment with diethylaminosulphurtrifluoride (DAST) in the presence of zinc iodide as catalyst (Scheme 1). Unfortunately, in our hands, this procedure was not reproducible with thioanisole (8) also being produced [ratios of (7):(8) varied from 100:0 to 0:100]. Only when the reaction was carried out in the absence of catalyst could an acceptable transformation be achieved. Conversion into the required fluorosulphoximine reagent (4) was then accomplished by the method of Johnson[5].

Scheme 1

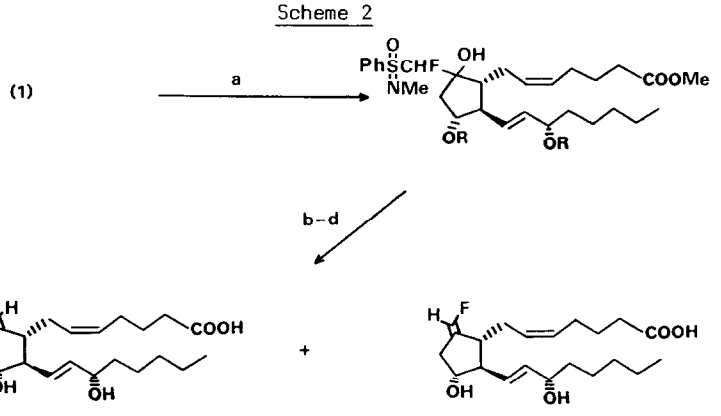


a. DAST/$CHCl_3$/50°; 99%
b. mCPBA/$CHCl_3$; 96%
c. $NaN_3/H_2SO_4/CHCl_3$; 98%
d. (i) $Me_3O^+BF_4^-/CH_2Cl_2$; (ii) NaOH; 56%

As anticipated, addition of an aldehyde or ketone to a solution of the sulphoximine (4) (1.2→1.5eqs) which had been deprotonated with lithium diisopropylamide (LDA) (THF, -78°→-90°) afforded the adducts (5) in excellent yields. Subsequent conversion into the fluoro-olefins (6) with aluminium amalgam gave satisfactory results for aromatic and aliphatic aldehydes and for aliphatic and alicyclic ketones (Table, entries 1-4). Aromatic and α,β-unsaturated ketones however afforded variable amounts of fluoro-olefin (6), fluorohydrin (9) or no isolable product (entries 5-7).

Despite the observed variablity, and confirming the mildness of this new methodology, the ketoacid (1) was satisfyingly converted into the desired E- and Z-fluoromethylene PGE_2 (3a,b)[9] in acceptable yield (Scheme 2).

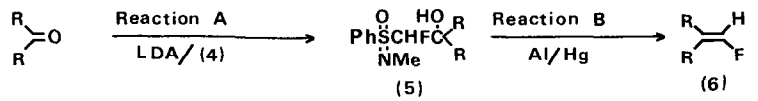
Scheme 2

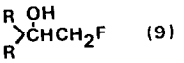


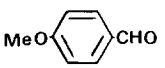
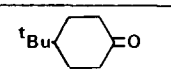
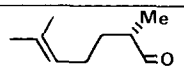
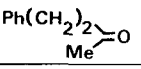
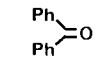
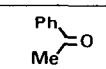
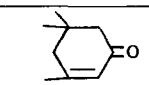
(3a) 9-E (3b) 9-Z

a. (i) (4)/LDA (ii) CH_2N_2; 100%
b. Al/Hg/THF/H_2O/AcOH; 57%
c. HF/MeCN; 9-E, 37% + 9-Z, 40%
d. aq.NaOH/MeOH; (3a,b) both 100%

TABLE





	SUBSTRATE	REACTION	
		A: % YIELD (5)	B: % YIELD (6)
1.		79	61[a,b]
2.		95	68
3.		83	91[a]
4.		91	76[a]
5.		86	40[c]
6.		92	-[d]
7.		95	-[e]

a. 1:1 Mixture of E:Z isomers.
b. If Na/Hg is used in step B the fluorohydrin (9) is obtained; 57%.
c. Impure, contaminated with sulphur containing by-products. Fluorohydrin (9) also isolated; 36%.
d. No fluoro-olefin (6) obtained but impure fluorohydrin (9) isolated; 32%.
e. No identifiable products isolated although all adduct (5) is consumed.

Experimental Conditions for Reactions A and B; taken from entry 4

A. Sulphoximine (4) (360mg, 1.9mmol) in THF (2mℓ) was added to a solution of LDA (1.1 equivalents) in THF (2mℓ) at -85° under N_2. After 10mins a solution of benzylacetone (190mg; 1.28mmol) in THF (2mℓ) was added followed 30mins later by aqueous NH_4Cl (10mℓ). The product was extracted into ethyl acetate and purified by flash chromatography[10,11] on silica gel. Adduct (5) was isolated as a colourless oil (390mg; 91%).

B. Freshly prepared aluminium amalgam (from 200mg of Al foil) was added to a solution of the adduct (5) (200mg, 0.6mmol) in AcOH:THF:H_2O (15:15:1; 5mℓ). After agitating for 4hr the product was extracted into ether washed with 2N NaOH and isolated as in A. Fluoro-olefin (6) was obtained as a colourless oil (75mg, 76%).

Finally, the observation that the use of sodium amalgam[5] favours the formation of fluorohydrins (Table, note **b**) could be significant as these systems are often obtained by cleavage of the corresponding epoxides under quite drastic conditions[12].

Conclusions

α-Fluoromethyl-N-methyl-phenylsulphoximine (4) can be used to convert various aldehydes and ketones into the corresponding fluoro-olefins, under mild conditions. This process complements existing methodology[4] and is especially useful for base-sensitive molecules[13].

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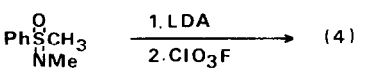
8. Fluorination of the parent sulphoximine only afforded a 20% yield of (4).



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9. The biological activity of (3a,b) will be reported separatly.
10. W. C. Still, M. Kahn and A. Mitra, J. Org. Chem., 1978, 43, 2923.
11. All new compounds possessed satisfactory spectroscopic and/or analytical data.
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13. This methodology has also been applied successfully to an extremely base-sensitive 3,4-dialkoxycyclopentanone. The description of this work will be the subject of a subsequent report.

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