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Synthesis of α-fluoro- and α,α-difluoro-benzenemethanesulfonamides: new inhibitors of carbonic anhydrase

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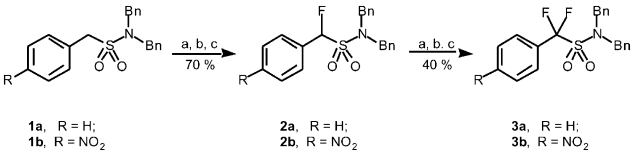
Direct fluorination of arenemethanesulfonamide anions under mild conditions and in high yield has been accomplished using *N*-fluorobisbenzenesulfonimide, NFSi, on carbanions of *N*-*tert*-butyl- and *N*-*bis*-(4-methoxyphenylmethyl)-benzenemethanesulfonamides giving novel α-fluoro- and α,α-difluoro-benzenemethanesulfonamides respectively: IC_{50} and pK_a data show that α-halogenation enhances sulfonamide acidity incrementally and correlates well with increased carbonic anhydrase inhibition, while lipophilicity is also enhanced.

α-Fluorination of alkanephosphonic acids was proposed as a strategy for improving their performance as stable bioisosteres for phosphate esters and anhydrides over 20 years ago.[1] Since then, α-fluoro- and α,α-difluoroalkanephosphonic acids have been widely deployed as isosteric and isopolar mimics of biological phosphates.[2] Increasingly safe and effective routes for their synthesis,[3] especially the use of *N*-fluorobisbenzenesulfonimide,[4] NFSi, have underpinned their wide application, initially as nucleotide analogues[5] and subsequently as peptidyl phosphate surrogates.[6] Such use of the CF_2 group as an isosteric and isopolar[1] replacement for a bridging oxygen in phosphate chemistry and biology has inspired its application to substitution of the furanose ring-oxygen in nucleosides[7] and, more recently, in mimics of aryl sulfate esters, particularly of estrone 3-sulfate.[8] However, the preparation and properties of α-fluoroarenemethanesulfonamides has not been explored hitherto, though the perfluoroalkanesulfonamides are well known,[9] and currently under investigation as environmental pollutants.[10]

Broad-based studies in sulfonamide inhibition of carbonic anhydrase, which have underpinned major developments in glaucoma therapy,[11] have linked increasing acidity of heteroarenesulfonamides and fluoroalkane-sulfonamides to their affinity for carbonic anhydrase, where the anionic sulfonamide nitrogen becomes a ligand for the catalytic zinc in the active site.[12,13] Unfortunately, Maren's discovery of the outstanding properties of trifluoromethanesulfonamide as a carbonic anhydrase inhibitor has been compromised by its poor bioavailability.[11] We therefore decided to undertake a systematic investigation of the effect of α-fluorination of arenealkane- and heteroarenealkanesulfonamides, seeking thereby to identify improved carbonic anhydrase inhibitors of enhanced acidity and greater lipophilicity.

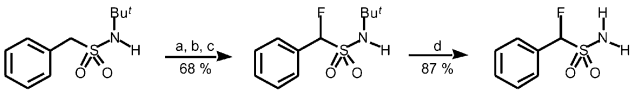
Surprisingly, the chemical literature is almost devoid of any description of the preparation of arenefluoroalkane-sulfonamides. After some experimental vicissitudes, we chose to focus on electrophilic fluorination of arenealkanesulfonamides using NFSi.[4] We soon found that partial or total protection of the sulfonamide nitrogen was required to achieve the necessary ionisation of the sulfonamide α-CH_2 group. Initial experiments with *N*,*N*-*bis*-phenylmethyl-(benzenemethane)sulfonamide (**1a**) and the corresponding 4-nitrobenzenemethanesulfonamide (**1b**) using sodium hexamethyldisilazide (NaHMDS, 1.1 equiv.) and NFSi (1.1 equiv.) in THF at −78 °C gave the respective protected arenemonofluoromethanesulfonamides (**2a** and **2b**) in 70% yield after flash chromatography. By using 2.2 equivalents of base and NFSi, the difluoromethanesulfonamides (**3a** and **3b**) were prepared directly in 40% isolated yield. Rather higher yields of these products were obtained by re-fluorination of the arenemonofluoromethanesulfonamides (**2a** and **2b**) (Scheme 1).



1a, R = H; **1b**, R = NO_2 **2a**, R = H; **2b**, R = NO_2 **3a**, R = H; **3b**, R = NO_2

Scheme 1 a) NaHMDS, 1.1 equiv., THF, −78 °C, 0.5 h; b) NFSi, 1.1 equiv., THF, −78 °C 6 h → rt; c) HCl aq.

Unfortunately, all attempts to remove the benzyl protecting groups by various reduction procedures proved fruitless. Similar problems have been reported previously.[14] We therefore turned to the use of the *tert*-butyl protecting group for the sulfonamide nitrogen. *N*-*tert*-Butyl-(benzenemethane)sulfonamide[15] (**4**) was treated with *n*-butyllithium (2.2 equiv.) followed by NFSi (2.2 equiv.) in THF at −78 °C to give *N*-*tert*-butyl-(benzene-fluoromethane)-sulfonamide (**5**) in 68% yield after flash chromatography. The *tert*-butyl group was readily removed on stirring with trifluoroacetic acid, TFA, at rt for 2 h to give benzenefluoro-methanesulfonamide (**6**) as a colourless crystalline solid in 87% yield (Scheme 2). All efforts to introduce a second fluorine either by repeated fluorination of (**5**) or by using a large excess of base and FSi on the starting material (**4**) were unsuccessful.



4 **5** **6**

Scheme 2 a) BuLi, 2.2 equiv., THF, −78 °C → 0 °C → −78 °C, 1 h; b) NFSi, 2.2 equiv, THF, −78 °C 10 h → rt; c) HCl aq., 0 °C; d) TFA, rt, 2 h.

We therefore chose to employ the 4-methoxyphenyl-methyl group to protect fully the sulfonamide. We prepared *N*-*bis*-(4-methoxyphenylmethyl)-benzenemethanesulfonamide (**7**), and established that it was easily converted into benzenemethanesulfonamide (**8**) on stirring with TFA at rt. Treatment of (**7**) with BuLi (1.1 equiv.) followed by TFSi (1.1 equiv.) at −78 °C in THF gave *N*-*bis*-(4-methoxyphenylmethyl)-benzene-fluoromethanesulfonamide (**9**) in 82% yield after crystallisation from ethanol. Benzenefluoromethanesulfonamide (**6**) was obtained on stirring (**9**) with TFA overnight (41%) or by oxidation of (**9**) with ceric ammonium nitrate (32%) in aqueous acetone. Stepwise, double fluorination of (**8**) with first 1.1 equiv. of base and NFSi followed by a second equivalent of base and of NFSi led to *N*-*bis*-(4-methoxyphenylmethyl)-benzene- difluoromethanesulfonamide (**10**) in 68% yield after crystallisation from ethanol. Deprotection using TFA provided benzenedifluoromethanesulfonamide (**11**) as white crystals from

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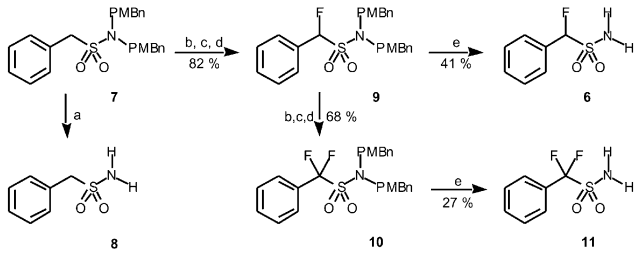

Scheme 3 a) TFA, rt, 2 h; b) BuLi, 1.1 equiv., THF, −78 °C, 0.5 h; c) NFSi, 1.1 equiv., THF, −78 °C 45 min → rt; d) $NaHCO_3$aq., rt; e) TFA, 16 h, rt. (PMBn, *p*-methoxybenzyl).

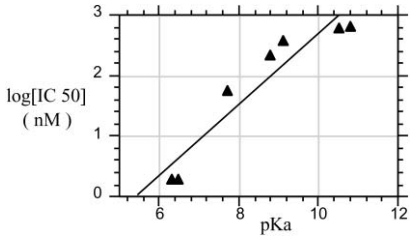

Fig. 1 Plot of log[IC_{50}] against pK_a for the seven sulfonamides listed in Table 1. Linear regression analysis (Kaleidagraph™) gives slope of +0.59, $R = 0.945$.

ether (27%). These results constitute the first rational syntheses of monofluoro- and difluoroarenemethanesulfonamides (Scheme 3).[16]

The pK_a values of these and other select sulfonamides (Table 1) were determined by potentiometric titration at 37 °C in water at ionic strength 0.1. Partition coefficients, P_{ether}, were measured spectroscopically for the equilibrium ether : water (pH 7.2) at 25 °C; and IC_{50} values for inhibition of carbonic anhydrase (Bovine type II, Boehringer Mannheim) were determined at 3 °C and pH 7.2 by pH stat titration.[17] These data clearly show first, that α-fluorination of sulfonamides directly delivers increased sulfonamide acidity (Table 1). Secondly, there is a direct linear correlation between pK_a and log(IC_{50}) over four decades of acidity showing that α-fluorination of alkanesulfonamides is directly linked to both of these values (Fig. 1). Notably, difluorination of (**8**) increases its CAI 11-fold. Thirdly, since both benzenefluoromethanesulfonamide (**6**) and benzenedifluoromethane-sulfonamide (**11**) have good water solubility (in excess of 30 g dm^{-3} at pH 7.2), while their hydrophobicity has increased significantly relative to that of (**8**), it is evident that there is excellent scope for the further deployment of the CF_2 function to generate improved sulfonamide inhibitors of carbonic anhydrase with adequate water-solubility for topical use in glaucoma therapy.

Table 1 Physical data for a range of alkane- and arenealkane-sulfonamides

Compound	pK_a	IC_{50}/nM	P_{ether}
$CH_3SO_2NH_2$	10.8 ± 0.15	650 ± 40	—
$PhCH_2SO_2NH_2$ (**8**)	10.5 ± 0.10	630 ± 25	1.2 ± 0.20
$CH_2ClSO_2NH_2$	9.1 ± 0.1	390 ± 20	—
$PhCHFSO_2NH_2$ (**6**)	8.80 ± 0.05	220 ± 10	5.65 ± 0.20
$PhCF_2SO_2NH_2$ (**11**)	7.70 ± 0.05	58 ± 4	13.0 ± 0.20
$C_4F_9SO_2NH_2$	6.50 ± 0.10	<2	—
$CF_3SO_2NH_2$	6.30 ± 0.05	<2	0.003

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