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# Electrophilic Fluorination in the Synthesis of new Fluoroindoles

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***Abstract:*** *Fluorination of trialkylstannylindoles with caesium fluoroxysulfate or Selectfluor™ was investigated for the synthesis of* inter-alia *2- and 3-fluoroindoles. Caesium fluoroxysulfate gave good yields of these potentially useful intermediates; Selectfluor provided lower yields.*

The development of new methods for the selective fluorination of molecules is of great interest to chemists in general, and medicinal chemists in particular, as the combination of potent electronic properties and negligible steric demands makes fluorine substitution a useful tool[1]. In biologically active compounds metabolism may be blocked, potency enhanced or sites of hydrogen bonding probed for with a judiciously placed fluorine substitutent[2]. Fluorinated analogues of natural products often serve as suicide inhibitors of enzymic processes whilst $^{18}$F-substituted compounds have seen extensive use in Positron Emission Tomography[3].

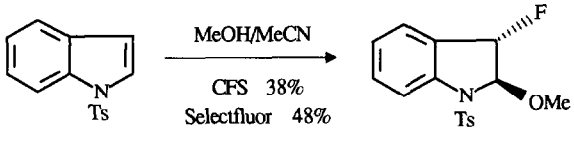
Although sources of nucleophilic fluorine have been developed to the extent that reagents such as DAST and its analogues see extensive use in synthetic organic chemistry, few reagents that act as sources of electrophilic fluorine have become sufficiently easy to handle for their use to be commonplace. However several milder reagents for electrophilic fluorination have recently come to light; particularly interesting are the N-fluoro-diazabicyclics[4] and sulfonamides[5], xenon difluoride[6] and caesium fluoroxysulfate (CFS)[7].

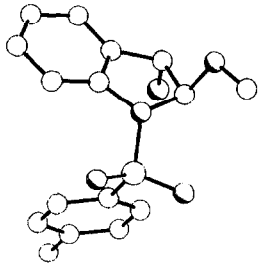
The advantage of these newer reagents lies in their relatively weak fluorinating power- if the desired site of substitution needs to be activated for fluorination to occur there is scope for selectivity. The approach that we[8], and others[9], have taken is to match the fluorinating reagent to a substrate functionalised as an organometallic derivative at the desired site of substitution. In this paper we report our results for the fluorination of trimethylstannyl derivatives of indoles, using caesium fluoroxysulfate or Selectfluor as the source of electrophilic fluorine.

Indole-ring containing compounds are widespread in nature, the essential amino acid *L*-tryptophan being utilised in the biosynthesis of molecules as diverse as the neurotransmitter serotonin and complex alkaloids such as the ergolines. This has led medicinal chemists to synthesise many compounds containing this ring system as potential therapeutic agents or tools for pharmacological research. Most syntheses of indoles employ a suitably substituted benzene ring as starting material and use various techniques to form the pyrrole ring. These methods are generally quite tolerant of substitution in the benzene ring and all of the common halogens can be incorporated into this portion of the indole system simply by using the relevant starting material.

In comparison, the scope for synthesising indoles halogenated in the pyrrole ring is much smaller. Bromination and iodination of indoles occurs preferentially at the 3-position[10]. The 2-position of the indole ring has been halogenated by electrochemical techniques[11] or through the use of a 2-lithio species to give chloro, bromo or iodo substitutuion[12]. To date no method for the direct synthesis of 2-fluoro or 3-fluoro indoles has been published. Barton and co-workers synthesised some fluoroindolines by the addition of trifluoromethyl hypofluorite to the 2,3-double bond of the pyrrole ring; subsequent elimination with base yielded a fluorinated indole[13].

Initially we investigated the fluorination of 1-substituted indoles with CFS or Selectfluor in acetonitrile or acetonitrile/methanol solvent mixtures. Using acetonitrile alone as solvent resulted in complex reaction mixtures with no single fluorinated product predominating. However, the addition of small quantities of methanol to the reaction mixture resulted in clean conversion of 1-(4-toluenesulfonyl)indole into 3-fluoro-2-methoxy-1-(4-toluenesulfonyl)indoline in 38% isolated yield with CFS and 48% with Selectfluor. Relative stereochemistry about the 2,3-bond in the pyrrolidine ring was confirmed as *trans* by X-ray crystallographic analysis[14] (Scheme 1).

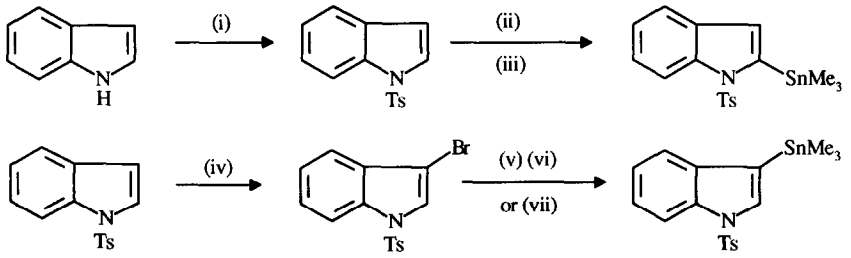


**SCHEME 1**

This result might be expected from the known tendency of indoles to undergo electrophilic substitution at the 3-position, and is in agreement with observations on the reactivity of CFS[15] and Selectfluor[16] with alkenes in the presence of methanol. In order to achieve regioselective fluorination, without concomitant substitution by a nucleophile, we decided to investigate the *ipso* directing ability of an organometallic species in electrophilic fluorination. Trialkylstannyl substitution has been used for directing such reactions[8] so we synthesised 2- and 3-trimethylstannylated -1-(4-toluenesulfonyl)indoles.

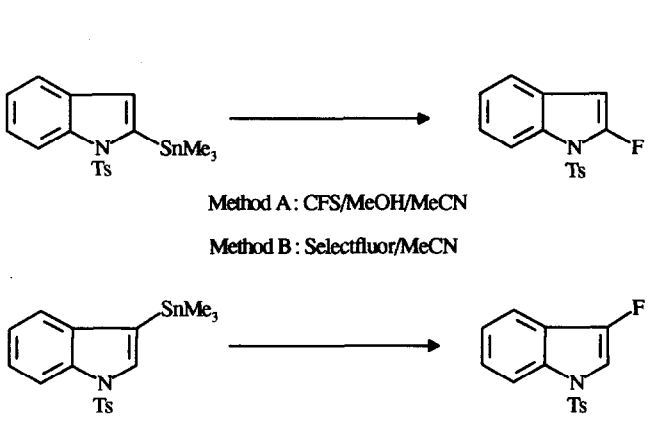
1-(4-Toluenesulfonyl)indole was lithiated with LDA[17] and quenched with trimethylstannyl chloride to give a 2-trimethylstannylindole. The corresponding 3-trimethylstannylindole was prepared *via* lithiation of 3-bromo-1-substituted indole with t.BuLi[18] and similar work up or *via* a palladium catalysed coupling reaction with hexamethylditin[19] (Scheme 2).




Reagents: (i) KOH, 4-TsCl, $H_2O$, toluene; (ii) LDA, THF; (iii) $Me_3SnCl$; (iv) $Br_2$, $CCl_4$; (v) t.BuLi, THF; (vi) $Me_3SnCl$; (vii) Tetrakistriphenylphosphine palladium(0), $(Me_3Sn)_2$, toluene.

**SCHEME 2**

Fluorination of trialkylstannylindoles was attempted under a range of conditions for each fluorinating reagent. Although changing the temperature made a small difference to the yields the most important factor was the solvent employed. For reactions employing CFS, acetonitrile alone as solvent gave poor yields of fluoroindoles. However, the presence of methanol in the reaction mixture gave a much cleaner reaction with both 2- and 3-trimethylstannyl-1-(4-toluenesulfonyl)indole undergoing fluorination to give the corresponding fluoroindole in 61% and 72% yield respectively (*Method A*). For reactions employing Selectfluor we found that only reactions conducted in neat acetonitrile gave any of the desired products (2-fluoro in 40% yield and 3-fluoro in 21% yield, *Method B*): addition of methanol resulted in products incorporating a methoxy group as well as fluorine and use of DMF resulted in only hydro-destannylated indoles. In the fluorination of 2-trimethylstannyl indole with Selectfluor the main side reaction was the formation of 2,3-difluoroindole.




**SCHEME 3**

These results indicate that the *ipso* directing abilities of an organometallic species can be used in conjunction with electrophilic fluorinating reagents to overcome the usual preference for indoles to react with electrophiles in the 3-position, thus providing access to novel fluoroindoles which may be of great interest as intermediates to drug candidates. In this particular application caesium fluoroxysulfate provides superior yields to, and fewer by-products than, the commercially available reagent, Selectfluor.

## EXPERIMENTAL

**Materials and General Procedures:**

Melting points were recorded on a Gallenkamp MFB apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC (200 MHz) and a Bruker AMX (600MHz). Chemical shift values are given in ppm downfield from TMS for $^{1}H$ data and from $CFCl_3$ for $^{19}F$ data. Coupling constants are given in Hertz. Mass spectra are EI (Concept32, Kratos) or FAB (MS50, Kratos). High resolution mass spectra were recorded on a Concept32 using EI technique. Column chromatography was carried out on Merck silica gel mesh size 0.04-0.06mm., employing cyclohexane/ether mixtures as eluent, with 1% triethylamine added when purifying trimethylstannyl indoles. Solvents were dried and distilled prior to use. Caesium fluoroxysulfate was prepared by the method of Appelman[20] and Selectfluor was purchased from Air Products and Chemicals PLC. All other starting materials were obtained from Aldrich Chemical Co.

**1-(4-Toluenesulfonyl)indole**

Indole (4.7g, 40mM) was added to toluene (80ml) with stirring under nitrogen. Tetrabutylammonium hydrogen sulfate (1g) was added followed by aqueous potassium hydroxide (50%, 50ml) and the mixture stirred rapidly. A solution of 4-toluenesulfonylchloride (8g, 42mM) in toluene (80ml) was added and the mixture stirred for 3 hours. The organic layer was separated and washed with water (3x250ml), dried over sodium sulfate and evaporated to give a tan solid which was re-crystallised from ethanol to give white plates

(7g, 65%). Mp. 85°C (Lit.[21] 86°C). $\delta_H$ (200MHz, $CDCl_3$): 2.33 (3H, s, $CH_3$), 6.64-6.66 (1H, d, 3-H, *J* 3.7 Hz), 7.18-7.23 (2H, d, Ar *J* 8.4 Hz), 7.25-7.35 (2H, m, 5-H, 6-H), 7.50-7.55 (1H, m, 4-H), 7.56-7.58 (1H, d, 2-H, *J* 3.7 Hz), 7.74-7.78 (2H, d, Ar, *J* 8.4 Hz), 7.98-8.02 (1H, d, 7-H, *J* 8 Hz).

**3-Bromo-1-(4-toluenesulfonyl)indole**

Carbon tetrachloride (50ml) was stirred under nitrogen at room temperature and 1-(4-toluenesulfonyl)indole (3g, 11mM) was added. A solution of bromine (0.70ml, 13.6mM) in carbon tetrachloride (50ml) was added dropwise over 30 minutes and stirring continued for 2 hours. The dark solution was poured onto saturated aqueous sodium bicarbonate (100ml) and the organics separated, washed with aqueous sodium thiosulfate then brine, dried over sodium sulfate and evaporated. Crystallisation from ethanol gave white needles (3.1g, 80%). Mp. 119-120°C (Lit.[22] 120-123°C). $\delta_H$ (200MHz, $CDCl_3$): 2.34 (3H, s, $CH_3$), 7.21-7.25 (2H, d, Ar, *J* 8 Hz), 7.30-7.51 (2H, m, 5-H, 6-H), 7.48-7.51 (1H, d, 4-H, *J* 6.6 Hz), 7.62 (1H, s, 2-H), 7.75-7.79 (2H, d, Ar, *J* 8 Hz), 7.97-8.02 (1H, d, 7-H, *J* 8 Hz).

**1-(4-Toluenesulfonyl)-3-trimethylstannylindole**

To a solution of 3-bromo-1-(4-toluenesulfonyl)indole (1.25g, 3.6mM) in dry toluene (50ml) was added hexamethylditin (1.25g, 4.2mM), followed by tetrakistriphenylphosphinepalladium(0) (100mg). The mixture was heated to reflux under nitrogen for 6 hours, cooled and evaporated, then purified by chromatography to give 800mg (50%) of the required product as a white powder. Mp. 120-122°C. (Found: C, 50.33; H, 4.81; N, 3.10; $M^+$ 435 (Sn=120). $C_{18}H_{21}NO_2SSn$ requires: C, 49.80; H, 4.84; N, 3.23%; $M^+$ 435 ). $\delta_H$ (200MHz, $CDCl_3$): 0.26-0.55 (9H, t, $SnMe_3$, *J* 56 Hz), 2.33 (3H, s, $CH_3$), 7.20-7.32 (4H, m, 2Ar, 5-H, 6-H), 7.47 (1H, s, 2-H), 7.48-7.52 (1H, d, 4-H, *J* 7.5 Hz), 7.78-7.83 (2H, d, Ar, *J* 8.5 Hz), 7.98-8.02 (1H, d, 7-H, *J* 8 Hz).

This material was also prepared by adding t.BuLi (1.7M in pentane, 7ml, 11.9mM) dropwise to a THF (50ml) solution of 3-bromo-1-(4-toluenesulfonyl)indole (2g, 5.7mM) at -70°C. Stirring was continued at -70°C for 30 minutes and a solution of trimethylstannyl chloride (1.2g, 6mM) in THF (30ml) was added dropwise. The solution was stirred and allowed to warm to room temperature overnight then saturated aqueous potassium fluoride (25ml) was added and the organic phase separated, dried over sodium sulfate and evaporated. Chromatography gave 1-(4-toluenesulfonyl)-3-trimethylstannylindole (2.1g, 85%) as a white powder.

**3-Fluoro-1-(4-toluenesulfonyl)indole**

*Method A* Dry methanol (5ml) and dry acetonitrile (10ml) were stirred under nitrogen and 1-(4-toluenesulfonyl)-3-trimethylstannylindole (100mg, 0.25mM) was added. The solution was cooled in an ice bath and CFS (75mg, 0.3mM) was added in one portion. The mixture was allowed to warm to room temperature overnight and then some precipitate filtered off and the filtrate purified by chromatography to give 3-fluoro-1-(4-toluenesulfonyl)indole (52mg, 72%) as a white powder. Mp. 87-88°C. (Found: C, 62.36; H, 4.23; N, 4.75; $M^+$ 289, HR mass 289.0588. $C_{15}H_{12}FNO_2S$ requires: C, 62.28; H, 4.15; N, 4.84%; $M^+$ 289, HR mass 289.0591). $\delta_H$ (200 MHz, $CDCl_3$): 2.34 (3H, s, $CH_3$), 7.15-8.10 (9H, m, aryl). $\delta_F$ (564 MHz, $CDCl_3$): -165 (1F, t, 3-F, *J* 2.6, 2.6 Hz).

*Method B* A solution of 1-(4-toluenesulfonyl)-3-trimethylstannylindole (500mg, 1.15mM) in dry acetonitrile (20ml) was stirred under nitrogen at room temperature. Selectfluor (500mg, 1.15mM) was added in one portion and the solution stirred for 12 hours. After 3 hours a white precipitate began to appear. The mixture was filtered and the filtrate evaporated. 3-Fluoro-1-(4-toluenesulfonyl)indole (70mg, 21%) was isolated by chromatography. This material was identical to a sample prepared by *Method A*.

**1-(4-Toluenesulfonyl)-2-trimethylstannylindole**

A solution of lithium di-isopropylamide in THF was prepared in the usual way from di-isopropylamine (11.25mM) and butyl lithium (10.5mM) at -10°C then cooled to -70°C under nitrogen. A THF solution of 1-(4-toluenesulfonyl)indole (2.71g, 10mM) was then added dropwise. Stirring was continued at this temperature for 1 hour then a THF solution of trimethylstannylchloride (2.1g, 10.5mM) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight then diluted with saturated aqueous potassium fluoride and the organic layer separated, dried over sodium sulfate and evaporated. Flash chromatography gave the title product (3.42g, 79%), as a clear oil, which slowly solidified on standing. Mp. 68°C. (Found: C, 49.74; H, 4.91; N, 3.11; $M^+$ 435 (Sn=120). $C_{18}H_{21}NO_2SSn$ requires: C, 49.80; H, 4.84; N, 3.23%; $M^+$ 435). $\delta_H$ (200 MHz, $CDCl_3$): 0.45 (9H, m, $SnMe_3$), 2.32 (3H, s, $CH_3$), 6.84 (1H, s, 3-H), 7.10-7.15 (4H, m, Ar), 7.45-7.55 (3H, m, Ar), 7.80-7.90 (1H, m, 7-H).

**2-Fluoro-1-(4-toluenesulfonyl)indole**

*Method A* A solution of 1-(4-toluenesulfonyl)-2-trimethylstannylindole (380mg, 0.88mM) in dry acetonitrile (10ml) was diluted with dry methanol (5ml) and cooled in an ice bath under nitrogen. Caesium fluoroxysulfate (250mg, 1.0mM) was added in two portions and the reaction stirred and warmed to room temperature overnight. The resulting suspension was filtered and evaporated then purified by flash chromatography to give the title product as a white powder (155mg, 61%). Mp. 81°C. (Found: C, 62.20; H, 4.22; N, 4.77; $M^+$ 289. $C_{15}H_{12}FNO_2S$ requires: C, 62.28; H, 4.15; N, 4.84%; $M^+$ 289). $\delta_H$ (200MHz, $CDCl_3$): 2.36 (3H, s, $CH_3$), 5.94 (1H, d, 3-H, *J* 3 Hz), 7.15-7.45 (5H, m, Ar), 7.75-7.84 (2H, d, Ar, *J* 8 Hz), 8.05-8.14 (1H, d, 4-H, *J* 8 Hz). $\delta_F$ (564MHz, $CDCl_3$): -126 (1F, d, *J* 3 Hz).

*Method B* A solution of 1-(4-toluenesulfonyl)-2-trimethylstannylindole (500mg, 1.15mM) in dry acetonitrile (20ml) was stirred under nitrogen at room temperature. Selectfluor (500mg, 1.15mM) was added in one portion and the solution stirred for 12 hours. After 3 hours a white precipitate began to appear. The mixture was filtered then the filtrate evaporated and 2-fluoro-1-(4-toluenesulfonyl)indole (132mg, 40%) was isolated by chromatography. This material was identical to a sample prepared by *Method A*. Also isolated was 2,3-difluoro-1-(4-toluenesulfonyl)indole (85mg) (data given). Mp. 98°C. (Found: C, 58.55; H, 3.60; N, 4.45; $M^+$ 307. $C_{15}H_{11}F_2NO_2S$ requires: C, 58.63; H, 3.58; N, 4.56%; $M^+$ 307). $\delta_H$ (200MHz, $CDCl_3$): 2.38 (3H, s, $CH_3$, *J* 8 Hz), 7.20-7.50 (5H, m, Ar), 7.75 (2H, d, Ar, *J* 8 Hz), 8.13 (1H, d, 7-H, *J* 7 Hz). $\delta_F$ (564MHz, $CDCl_3$): -143 (1F, d, 2-F, *J* 8.5 Hz), -180.5 (1F, d, 3-F, *J* 8 Hz).

**Fluorination of 1-(4-toluenesulfonyl)indole**

A solution of 1-(4-toluenesulfonyl)indole (300mg, 1.1mM) in methanol (10ml) and acetonitrile (10ml) was cooled in an ice bath under nitrogen. Either CFS (360mg, 1.44mM) or Selectfluor (630mg, 1.45mM) was added and the mixture stirred and allowed to warm to room temperature overnight. The reaction mixture was filtered and evaporated then purified by chromatography to give *trans* 2,3-dihydro-3-fluoro-2-methoxy-1-(4-toluenesulfonyl)indole as the main product (135mg, 38% for CFS; 170mg, 48% for Selectfluor). Mp. 119°C. (The stereochemistry was assigned by X-ray crystallographic analysis[14]). (Found: C, 59.82; H, 5.14; N, 4.32; $M^+$ 321. $C_{16}H_{16}FNO_3S$ requires: C, 59.81; H, 4.98; N, 4.36%; $M^+$ 321). $\delta_H$ (200 MHz, $CDCl_3$): 2.32 (3H, s, $-CH_3$), 3.64 (3H, s, OMe), 5.33 (1H, d, CHF, *J* 55 Hz), 5.48 (1H, d, CHOMe, *J* 15 Hz), 7.05-7.70 (8H, m, aryl). $\delta_F$ (564MHz, $CDCl_3$): -165.2 (1F, dd, 3-F, *J* 55,15 Hz).

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