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A facile transfer fluorination approach to the synthesis of *N*-fluoro sulfonamides

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Abstract

The synthesis of *N*-fluoro sulfonamides can be readily accomplished by the transfer fluorination of the potassium salt of the sulfonamide with the readily available, solid fluorinating agent, *N*-fluoro benzenesulfonimide. The fluorination requires no special equipment or techniques, and is both rapid and general. © 2000 Published by Elsevier Science Ltd. All rights reserved.

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The replacement of hydrogen with fluorine in biologically active molecules has stimulated the development of new methodology for the construction of fluorinated compounds. Studies of the interactions of these fluorinated molecules with biological systems have shown unique novel characteristics.[1] The extreme electronegativity of fluorine uniquely influences the basicity, acidity, and non-bonding interactions of neighboring groups, as well as allowing the fluorine to act as a hydrogen bond acceptor.[2] The combination of the larger van der Waals radii of fluorine than hydrogen (1.47 versus 1.20 Å, respectively[3]) and the shorter bond length of C–F compared to C–H (1.39 versus 1.43 Å[4]) makes fluorine one of the best isosteric replacements for hydrogen. In addition, the high C–F bond strength and the electronegativity of fluorine decreases the metabolic transformations that fluorinated molecules can undergo, generally leading to more stable and pharmacologically useful compounds.[1]

We are interested in the synthesis of fluorinated agonists and antagonists of the thromboxane A_2 (TXA_2) receptor, with the intention of studying the interactions of the fluorinated moieties of the ligand with the receptor. One specific objective is to investigate the incorporation of *N*-fluoro sulfonamides, a suprisingly stable member of the *N*-halo sulfonamide family, into TXA_2 antagonists.[5,6] For this purpose we needed a facile, safe method for the synthesis of *N*-fluoro sulfonamides (Barnette reagents[5,6]): in short, a synthesis that does not utilize elemental fluorine.[6] We decided to limit our choice of fluorinating agents to those that are commercially available and very stable (Fig. 1): *N*-fluoro benzenesulfonimide (NFSi), *N*-chloromethyl-*N*′-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) ($F{\cdot}TEDA{\cdot}BF_4$), and *N*-

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fluoro-2,4,6-trimethylpyridinium triflate (NFTPT).[7] In this paper we report a general synthesis of *N*-fluoro sulfonamides based on a unique nitrogen-to-nitrogen transfer fluorination.[6,8]

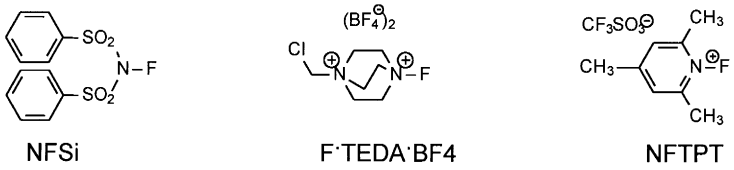
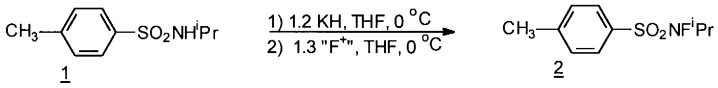


Fig. 1.

NFSi, F·TEDA·BF_4, and NFTPT have higher fluorination potentials than the *N*-fluoro sulfonamides and thus should be able to fluorinate neutral sulfonamides.[9] However, attempts to use these reagents to fluorinate the neutral *N*-isopropyl toluenesulfonamide failed to give the desired product. Recognizing that the system might need to be activated in order to induce fluorination at the nitrogen atom, we explored the reaction of the sulfonamide anion with the fluorinating reagents. Activation of the sulfonamide by conversion to the potassium salt, followed by reaction with the fluorinating reagents gave low yields of the *N*-fluoro, *N*-isopropyl toluenesulfonamide along with considerable recovery of the sulfonamide (i.e. 78-85%) as shown in Table 1.

Table 1

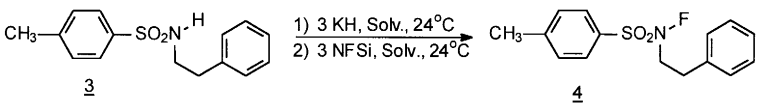


1 2

"F+"	NFSi	F·TEDA·BF_4	NFTPT
% yield of 2	15%[10]	No Reaction	No Reaction

In an effort to improve the yield of fluorination, we investigated some of the parameters that might influence the reaction. Since the temperature of the reaction might be important, we studied the fluorination in THF at temperatures between -78°C and 50°C. There was no change in the yield of the desired fluorinated product in this temperature range. Subsequent experiments were performed at ambient temperature for reasons of convenience. Since electrophilic fluorination has been observed to be sensitive to the cations used,[8c,8e,11] we also examined the effects of utilizing different salts. Unfortunately, we did not find significant differences between the fluorination of the Li, Na, and K salts of *N*-isopropyl toluenesulfonamide (12, 13, and 15% yields were obtained, respectively). However, since the potassium salt gave the fewest side-products, it was used in the subsequent experiments. It has been reported that anionic fluorination reactions demonstrate significant solvent effects.[5] With this in mind, we explored the fluorination of *N*-phenethyl toluenesulfonamide as a function of the polarity of the reaction solvent. We observed a large solvent effect in this transfer fluorination, in agreement with the literature (Table 2).

Table 2



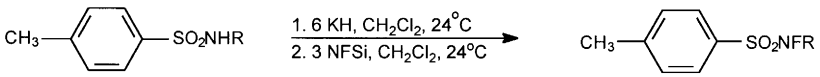
3 4

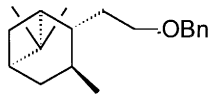
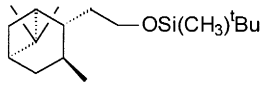
Solvent	CH_3CN	THF[12]	Toluene	CH_2Cl_2
% Yield of 4	6	38	48	53

Since the *N*-H sulfonamide was recovered in all of the reaction conditions explored,[10] we investigated the optimization of the ratio of base and fluorinating agent relative to the sulfonamide. We found the use of 3 equiv. of NFSi and between 3-6 equiv. of KH gave the optimal yield of fluorinated sulfonamides.

Having identified a set of optimized conditions for fluorination,[14] our interest was directed towards exploring the generality of the reaction. As seen in Table 3, the reaction is general and gives good to moderate yields of the desired *N*-fluoro sulfonamides. Clearly, the need for 6 equiv. of KH limits the functionality that can be present in the molecule. Within this restriction, the reaction allows sterically hindered sulfonamides to react cleanly to form the *N*-fluoro sulfonamide. Unhindered sulfonamides, however, suffer from competing nucleophilic attack at the sulfonyl group of the sulfonimide. Presumably this latter problem might be curtailed by utilizing other *N*-fluoro sulfonimides.

Table 3



R	Yield, %	^{19}F NMR ppm (multiplicity, J_{H-F} Hz)
Et	34	-53.28 (t, 40)
CH_2CH_2Ph	53	-50.31 (t, 40)
^{i}Propyl	95	-76.32 (t, 37)
^{c}Propyl	ND[13]	NA
^{t}Butyl	55	-62.96 (s)
	48	-78.00 (d, 51.7)
	70	-77.90 (d, 51.6)

We feel that the methodology presented here represents a significant improvement over methods currently available for the synthesis of *N*-fluoro sulfonamides, especially since it does not require the specialized equipment, handling, or safety precautions that are frequently associated with fluorinations. With the simplicity of this methodology, we expect that the pharmaceutical and agricultural applications of *N*-fluoro sulfonamides will be more widely studied. We are currently applying this methodology to the preparation of thromboxane A_2 receptor ligands containing the *N*-fluoro sulfonamide. We will presently report the pharmacological nature of the *N*-fluoro sulfonamides in this system.

References

1. (a) *Fluorine in Bioorganic Chemistry*; Welch, J. T.; Eswarakrishnan, S., Eds.; John Wiley & Sons: New York, 1991. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996. (c) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y., Ed.; Kodanasha Ltd, Elsevier Biomedical Press: New York, 1982.
2. For opposing opinions on the ability of fluorine to act as a hydrogen bond acceptor, see: (a) Dunitz, J. D.; Taylor, R. *Chem. Eur. J.* **1997**, *3*, 989 and (b) Howard, J. A. K.; Hoy, B. J.; O'Hagan, D.; Smith, G. T. *Tetrahedron* **1996**, *52*, 12613.
3. (a) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441. (b) O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1997**, 645.
4. Carbon–Fluorine Compounds: Chemistry, Biochemistry and Biological Activities; Ciba Foundation Symposium, Associated Scientific Publishers: Amsterdam, 1972.

5. Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452.
6. For a recent review on fluorination, see: Lal, G. S.; Pez, G. P.; Syvert, R. G. *Chem. Rev.* **1996**, *96*, 1737.
7. We explored the following commercially available fluorinating agents: *N*-chloromethyl-*N*′-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, F·TEDA·BF_4, Aldrich); *N*-fluoro-2,4,6-trimethylpyridinium triflate (NFTPT, Aldrich); *N*-fluorobenzenesulfonimide (Accufluor, NFSi, Aldrich). A list of the commercial and non-commercial fluorinating agents, as of 1996, with their structures can be found in Ref. 6. We thank Dr. George Shia of AlliedSignal for the generous gift of NFSi.
8. To the best of our knowledge, this is the first report of a heteroatom-to-heteroatom transfer fluorination. For recent examples of other transfer (heteroatom-to-carbon) fluorinations, see: (a) Banks, E. R. E.; Besheesh, M. K.; Mohialdin-Khaffaf, S. N.; Sharif, I. *J. Fluorine Chem.* **1997**, *81*, 157. (b) Okaonya, J. F.; Johnson, M. C.; Hoffman, R. V. *J. Org. Chem.* **1998**, *63*, 6409. (c) Davis, A. F.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273. (d) Umemoto, T.; Nagayoshi, M.; Adachi, K.; Tomizawa, G. *J. Org. Chem.* **1998**, *63*, 3379. (e) Kotoris, C. C.; Chen, M.-J.; Taylor, S. D. *J. Org. Chem.* **1998**, *63*, 8052.
9. Christe, K. O. *J. Fluorine Chem.* **1984**, *25*, 269.
10. The sulfonamide was recovered in 83% yield in reactions when 1.2 equiv. of KH and 1.3 equiv. of NFSi were used. Quenching the fluorination reaction with methyl iodide under these conditions resulted in recovery of the *N*-H sulfonamide in a similar yield, indicating that there was no anion present at the end of the reaction. Direct reaction of the sulfonamide anion produced under these conditions with methyl iodide resulted in complete (>95%) conversion to the *N*-methyl sulfonamide, indicating that the experimental conditions gave complete deprotonation of the sulfonamide. The fluorinated sulfonamide was stable to the conditions of the reaction work-up (>90% recovery). The mechanism for formation of the recovered sulfonamide is not known.
11. (a) Differding, E.; Ofner, H. J. *Synlett* **1991**, 187; (b) Differding, D.; Duthaler, R. O.; Kreeiger, A.; Ruegg, G. M.; Schmit, C. *Synlett* **1991**, 395.
12. Reaction of the less hindered *N*-ethyl and *N*-phenethyl sulfonamides in THF gave the *N*-phenyl, *p*-tolyl sulfonimides as the major side products (21% in both reactions). The identities of these imides were secured by direct synthesis. This product is proposed to be formed by nucleophilic attack of the sulfonamide anion on the sulfonyl group, rather than at the fluorine, of the *N*-fluoro benzenesulfonimide.
13. Over nine products were formed in this reaction. This reaction was considered to be a test of the hypothesis that the mechanism of this fluorination is a Single Electron Transfer process (Ref. 6, page 1750). However, the results obtained are not conclusive.
14. A general procedure for the synthesis of *N*-fluoro sulfonamides is as follows: KH (2.84 mmol) and 2 mL of anhydrous CH_2Cl_2 were placed in a 25 mL round-bottomed flask and the mixture was stirred under an N_2 atmosphere. The sulfonamide (0.47 mmol) was dissolved in 2 mL of anhydrous CH_2Cl_2 and added to the KH slurry via cannula. The reaction mixture was stirred for 30 min at 24°C, at which time *N*-fluoro benzenesulfonimide (1.4 mmol, dissolved in 2 mL of anhydrous CH_2Cl_2, was added to the reaction via cannula. The reaction was stirred for a further 6 h at 24°C, which was followed by quenching with a NaOH–NH_4OH solution (2 g NH_4OH, 6.5 g NaOH, and 100 mL H_2O). The *N*-fluoro sulfonamide was extracted with diethyl ether (2×10 mL). The organic layers were combined and washed with the NaOH–NH_4OH solution (3×10 mL), 5% NaOH (w/w) (3×10 mL), and 10% aqueous HCl (3×10 mL). The organic phase was dried over $MgSO_4$, filtered, and solvent removed under reduced pressure. The products were isolated by preparative chromatography (SiO_2, 20% ethyl acetate/hexanes).