Synthesis and reactivity of [^{18}F]-*N*-fluorobenzenesulfonimide†

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A novel [^{18}F]NF reagent and two novel radiochemical transformations have been developed: [^{18}F]NFSi has been prepared from sodium dibenzenesulfonimide and reacted in the presence of silyl enol ethers and allylsilanes to deliver labelled fluorinated ketones and allylic fluorides respectively; the radiosynthesis of the fluorinated A ring of vitamin D_3 has also been completed with success.

The increasing use of positron emission tomography (PET) for clinical diagnosis, drug development and, more generally, biological research has prompted many chemists to develop new labelling or purification methods.[1] Amongst the commonly used positron-emitting isotopes, ^{18}F stands out because of its advantageous half-life of 110 minutes. In addition, the low positron energy of ^{18}F results in the formation of images of high resolution. Undoubtedly, electrophilic fluorination offers exciting opportunities to access ^{18}F-labelled compounds otherwise unreachable or difficult to prepare *via* nucleophilic fluorination.[2] Electrophilic fluorination with ^{18}F has been reported using elemental fluorine, trifluoromethyl or acetyl hypofluorite, perchloryl fluoride and xenon difluoride. Although fluorine chemists have focused much attention on the synthesis and reactivity of structurally diverse electrophilic fluoronitrogen reagents,[3] only a few ^{18}F-labelled NF fluorinating reagents are known to date. These include [^{18}F]-*N*-fluoropyridinium triflate,[4] [^{18}F]-1-fluoro-2-pyridone[5] and various [^{18}F]-*N*-fluoro-*N*-alkylsulfonamides, of which [^{18}F]-*N*-fluoro-*endo*-norbornyl-*p*-tolylsulfonamide was found to be the most reactive fluorinating reagent when used in the presence of Grignard and organolithium reagents.[6] The syntheses of the ^{18}F-labelled reagent *N*-fluorobistrifluoromethanesulfonimide and *N*-fluoro-*ortho*-benzenesulfonimide were also attempted but the resulting ^{18}F-labelled species were found to be unsuitable for subsequent fluorinations (Fig. 1).[7]

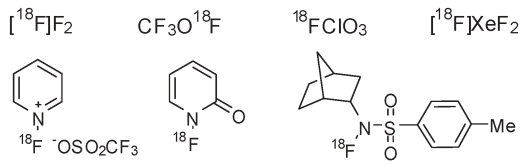

Fig. 1 ^{18}F-Labelled electrophilic fluorinating reagents.

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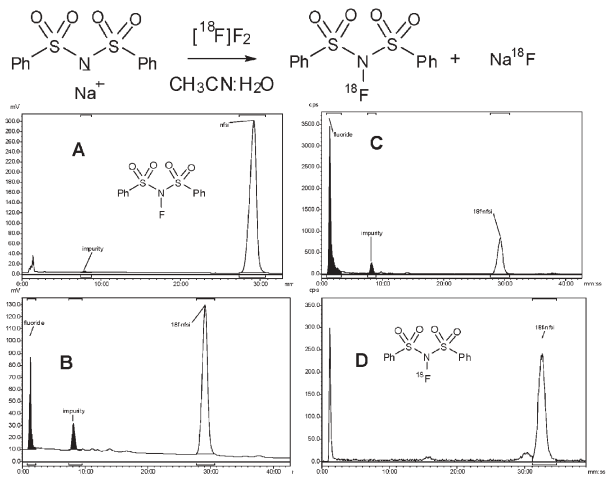
The availability of novel ^{18}F-labelled electrophilic fluorination reagents with improved characteristics will broaden the scope of radiochemical transformations and be of great value to all parties interested in PET. We initiated a research programme aimed at preparing additional labelled N–F reagents and at studying their reactivity with the aim of expanding the repertoire of available labelling processes. We focused our attention on *N*-fluorobenzenesulfonimide (NFSi), a compound prepared for the first time by E. Differding *et al.* and now commercially available.[8] NFSi is much more reactive than the currently available labelled N–F reagents and is commonly used to access various fluorinated compounds including drug-like targets.[9] More recently, NFSi was also found to be the most suitable reagent for various enantioselective organocatalyzed fluorinations.[10] Herein, we describe the first synthesis of [^{18}F]-*N*-fluorobenzenesulfonimide. We also investigated with representative transformations the suitability of this new labelled reagent for PET radiochemistry. These studies led to the development of two novel radiochemical reactions, the electrophilic fluorination of silyl enol ethers and of allylsilanes.

The original synthetic procedure to access NFSi involves the fluorination of $(PhSO_2)_2NH$ with 1 equivalent of fluorine (F_2/N_2, 10% w/w) in CH_3CN at −40 °C in the presence of powdered NaF in an ambient pressure reactor.[8] Slightly modified protocols were subsequently described in the literature using sodium dibenzenesulfonimide.[11] For the preparation of [^{18}F]NFSi (Scheme 1), we used [^{18}F]F_2 derived from the ^{18}O(p,n)^{18}F nuclear reaction using enriched [^{18}O]O_2 with 0.2% added F_2.[12] Typically, [^{18}F]F_2 was



Scheme 1 Synthesis of [^{18}F]-*N*-fluorobenzenesulfonimide. **A**: HPLC (millivolts (mV)) commercially available NFSi; **B**: HPLC (mV) crude [^{18}F]NFSi; **C**: HPLC (counts per second (cps)) crude [^{18}F]NFSi; **D**: HPLC (cps) [^{18}F]NFSi.

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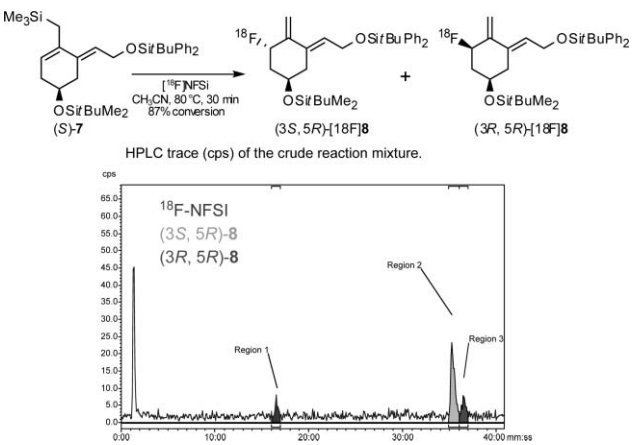
bubbled through a 0.01 M solution of $NaN(SO_2Ph)_2$ in CH_3CN–H_2O [9 : 1] for 10 min resulting in a crude stock solution of [^{18}F]NFSi [1–2 GBq].[13] Only trace amounts of [^{18}F]F_2 remained unreacted, confirming near maximum theoretical formation of [^{18}F]NFSi.

Radio-HPLC of the crude product revealed the formation of [^{18}F]NaF (t_r = 1.17 min) and [^{18}F]NFSi (t_r = 32.3 min) in a 1 : 1 ratio. The only other product observed was a minor impurity (t_r = 8.39 min, ~6%). The identity of [^{18}F]NFSi was confirmed by co-elution with the commercially available reagent. Following azeotropic drying, [^{18}F]NFSi was dissolved in anhydrous CH_3CN and used without further purification. Whilst [^{18}F]NFSi tolerates aqueous conditions, its reactivity is enhanced under anhydrous conditions. The total preparation time from end of bombardment was ~30 minutes, delivering [^{18}F]NFSi in a non-decay corrected yield of 40% of the total activity. The impurity, also present in trace amount in the commercially available reagent, was hardly detected on the HPLC trace of the sample recovered after drying. [^{18}F]NaF is present after drying but this salt does not interfere with the subsequent electrophilic fluorination.

Three model substrates were selected to test the reactivity of [^{18}F]NFSi, the trimethylsilylenol ether **1** derived from α-methyl tetralone and the two allylsilanes **2** and **3**. All starting materials were prepared according to literature procedures.[12,14] Their electrophilic fluorination was performed using 1 equiv. of cold NFSi in CH_3CN at 80 °C for up to 30 min and afforded good yields of the fluoroketone **4** and the allylic fluorides **5** and **6**, respectively (Table 1).[12]

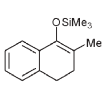
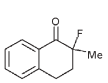
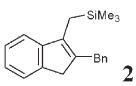
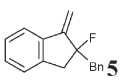
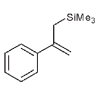
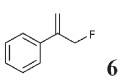
For the hot experiments, it was critical to use [^{18}F]NFSi in dry CH_3CN.[12] After addition of the fluorinating reagent to an excess of the substrate, the reaction mixture was stirred at 80 °C for up to 30 minutes. The crude mixture was analyzed using analytical HPLC by comparison with the trace of an authentic reference sample prepared independently using commercially available NFSi. The radiofluorination of the silyl enol ether **1** with [^{18}F]NFSi was successful, leading to [^{18}F]**4** uncontaminated by radiofluorinated side-products. The reaction was completed within 15 minutes at 80 °C. Purification by HPLC afforded [^{18}F]**4** in 51.2% yield [decay corrected] with a specific radioactivity of 4.3 MBq μmol^{-1} in line with the short irradiation time applied to the ^{18}O target.[13] The fluorination of the less nucleophilic allylsilane **2** was also remarkably efficient, leading to the allylic fluoride [^{18}F]**5** as the sole product (95% yield after 30 min). The radiofluorination of **3** was less efficient with only 35% of [^{18}F]NFSi converted into [^{18}F]**6** due to slower kinetics. Notably, no radioactive side-products were detected in the reaction mixture. We attempted next the radiosynthesis of the protected fluorinated dienol (3*S*,5*R*)-**8** from the corresponding dienylsilane (*S*)-**7** (Scheme 2).[15] Compound (3*S*,5*R*)-**8** is the 1α-fluoro-substituted A-ring fragment of an important fluorinated analogue of vitamin D_3.[16] Under our standard conditions, the radiochemical reaction proceeded smoothly to give 87% of the desired product as a mixture of two diastereomers (3*S*,5*R*)-[^{18}F]**8** (t_r = 34.35 min) and (3*R*,5*R*)-[^{18}F]**8** (t_r = 36.04 min) in a 4 : 1 ratio. The major product was the *anti* diastereomer as observed for the synthesis of the non-labelled material. The crude reaction mixture revealed the presence of [^{18}F]NaF, unconsumed [^{18}F]NFSi and the two expected fluorinated products as the only radioactive products.

In conclusion, [^{18}F]NFSi was prepared and used for the synthesis of ^{18}F-labelled compounds. To the best of our knowledge, these are the first radiochemical routes, using this reagent, to labelled allylic fluorides and α-fluorinated ketones from allylsilanes and silyl enol ethers respectively. The preparation of compound (3*S*,5*R*)-[^{18}F]**8** illustrated how this chemistry is applicable to the



Scheme 2 Radiolabelling of (*S*)-**7** with [^{18}F]NFSi.

Table 1 Reactions of NFSi and [^{18}F]NFSi with substrates **1–3**

Entry	Substrate	Product	NFSi Yield (%)[a]	[^{18}F]NFSi Yield (%)[b]
1	 **1**	 **4**	76	>99[c]
2	 **2**	 **5**	60	95[d]
3	 **3**	 **6**	57	35[d]

[a] Isolated yield. [b] Yield determined by analytical radio-HPLC integration. [c] 15 min at 80 °C. [d] 30 min at 80 °C.

radiolabelling of fluorinated drug-like structural motifs. [^{18}F]NFSi lends itself well to 'mix and shake' production protocols and does not require specialist equipment for labelling. All centres producing [^{18}F]F_2 are now in a position to transport and distribute a highly stable, reactive and selective electrophilic ^{18}F-fluorinating agent as a new tool for the synthesis of radiotracers. Current work in our laboratories investigates the scope and applicability of [^{18}F]NFSi with the synthesis of known and novel tracers and the results of these studies will be reported in due course.

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12 For details, see the Supporting Information.

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