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Synthesis of [^{18}F]Fluoroarenes via Nucleophilic Radiofluorination of *N*-Arylsydnones

Maruthi Kumar Narayanam, Gaoyuan Ma, Pier Alexandre Champagne, K. N. Houk, and Jennifer M. Murphy*

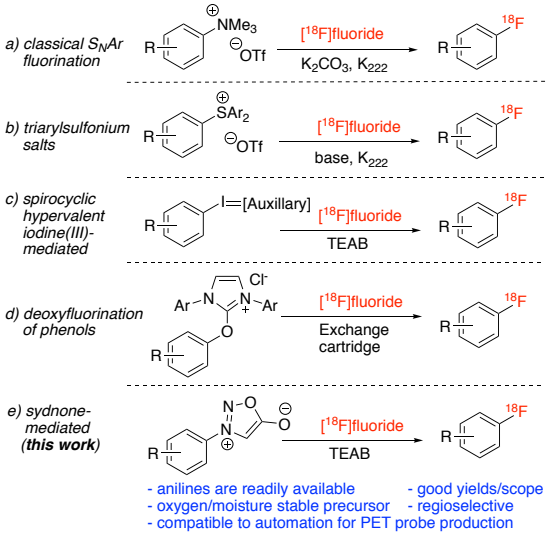
Abstract: A practical method for radiofluorination of anilines with [^{18}F]fluoride via *N*-arylsydnone intermediates is described. These precursors are stable, easy to handle and facilitate direct and regioselective ^{18}F-labeling to prepare [^{18}F]fluoroarenes. The value of this methodology is further highlighted by successful application to prepare an ^{18}F-labeled neuropeptide.

Positron emission tomography (PET) is emerging as a critically important, non-invasive in vivo imaging technique used for diagnosing, staging and therapy monitoring of disease.[1] The convenient half-life (110 min), high positron yield (97%), and broad availability of fluorine-18 (^{18}F) continue to make it the preferred radionuclide for clinical PET.[2] For decades the landscape of molecules easily accessible for widespread PET research has been limited by chemistry. Early approaches to afford [^{18}F]fluoroarenes from [^{18}F]fluoride were based on the Balz-Schiemann reaction via aryldiazonium salts.[3] Poor yields, competing fluoride incorporation from the BF_4^- counterion, and precursor instability has impeded wide adoption of this methodology for ^{18}F radiotracer preparation.[4] Recent advances in fluorination chemistry, particularly transition-metal-mediated methods to afford fluoroarenes, have soared dramatically in the last 5 years.[5] Fluorination with the radioisotope fluorine-18 has in turn significantly expanded the scope and diversity of ^{18}F-labeled small molecules.[4, 6] These metal-mediated methods offer approaches to previously inaccessible ^{18}F-labeled aromatics, thus increasing the potential radiochemical space for pre-clinical or clinical PET.[7] However, many methods rely on stoichiometric quantities of transition metals to forge the carbon-fluorine bond, require complex starting materials, or suffer from competing protonation side-reactions. Such characteristics pose practical challenges for automation on a commercial radiosynthesis platform and require difficult purification steps that affect the overall yield and reproducibility of these methods.

Despite the remarkable, recent developments in radio-fluorination, ^{18}F-labeled arenes are most frequently synthesized via nucleophilic aromatic substitution (S_NAr).[4] Trimethylanilinium triflates, triarylsulfonium salts,[8] diarylsulfoxides,[9] and diarylselenones[10] are typical precursors used in S_NAr reactions (Scheme 1). Diaryliodonium salts[11] are also viable precursors which give moderate to good selectivity that can be significantly improved with a copper catalyst.[12] Alternatively, spirocyclic iodonium ylides have demonstrated regioselective ^{18}F-fluorination with a broad substrate scope.[13] Recently, a concerted S_NAr reaction was reported to enable ^{18}F-deoxyfluorination of phenols via uronium intermediates.[14] However, competing formation of volatile [^{18}F]fluoromethane,[15] regioisomeric mixtures of ^{18}F-labeled products,[8a] challenging precursor preparation or requirement for expensive reagents can be limiting for these methods.

Sydnones are remarkably stable mesoionic heterocycles composed of an azomethine imine 1,3-dipole that, upon cycloaddition with alkynes and expulsion of CO_2, afford substituted pyrazole products.[16] From our previous experience constructing functionalized sydnones, we hypothesized that the electron-withdrawing nature of the 1,2,3-oxadiazole motif might enable activation of the attached aromatic ring for metal-free S_NAr chemistry. Arylsydnones are particularly attractive precursors for PET radiotracers as they can be readily prepared from inexpensive, commercially available anilines. Additionally, the mesoionic ring is stable to most chemical group manipulations, which allows for construction of functionally diverse precursors.

We report the development of a new method for the nucleophilic ^{18}F-fluorination of a broad range of aniline-derived *N*-arylsydnones (Scheme 1). These shelf-stable precursors can be handled in air, without special precautions, and their radiofluorination readily proceeds with [^{18}F]fluoride, without expensive stoichiometric reagents or transition-metal catalysts. In addition, we apply this methodology towards the synthesis of a sydnone prosthetic group and demonstrate rapid and facile ^{18}F-labeling of a commercial peptide via [3+2] cycloaddition.



Scheme 1. Modern, metal-free methods for ^{18}F fluorination of arenes.

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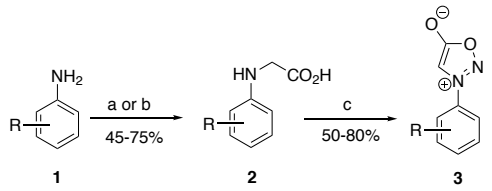
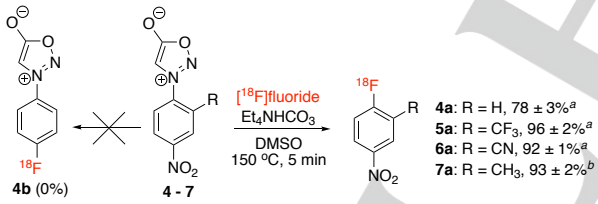
N-Arylsydnones are prepared in two steps from the appropriate anilines via initial formation of *N*-aryl glycines (Scheme 2).[17] Subsequent *N*-nitrosation and cyclodehydration of the resulting nitrosamines affords the mesoionic compounds in good yields.



Scheme 2. Preparation of *N*-arylsydnone precursors. Reagents and conditions: (a) ethyl bromoacetate, NaOAc, EtOH, reflux; LiOH, H_2O:THF (1:1), 0 °C; (b) NaOAc, AcOH, glyoxylic acid monohydrate, $NaBH_3CN$, MeOH, RT; (c) *t*Butyl nitrite, THF, trifluoroacetic anhydride, RT. THF = tetrahydrofuran.

We initially investigated ^{18}F-fluorination of 4-nitro-phenyl sydnone **4** because of the strongly activating nature of *para*-nitro substituents for S_NAr reactions. Radiofluorination of **4** proceeded in excellent radiochemical conversion (RCC) to afford [^{18}F]fluoro-4-nitrobenzene **4a** after 5 min at 150 ºC (Scheme 3). *Ortho* substitution was well tolerated, affording **5a** – **7a** in >92% RCC. For **5** and **6**, radiofluorination can also proceed at mild temperature (70 °C) in 68% and 72% RCC, respectively. Of note, formation of 4-[^{18}F]fluorophenyl sydnone **4b** via displacement of the nitro group was not detected, whereas sydnone displacement occurred readily. This selectivity resulted in a single radioactive product, and very clean HPLC traces, in all cases examined.



Scheme 3. Radiofluorination of *para*-nitro substituted *N*-arylsydnones. RCC was determined by radio-TLC. [a]n = 4. [b]n = 3. DMSO = dimethyl sulfoxide.

To understand the origin of this selectivity, we performed density functional theory (DFT) calculations at the M06-2X/6-311+G(d,p) level of theory,[18] using Gaussian 09 (Figure 1).[19] The SMD solvation model[20] for DMSO was used throughout the calculations. For the reaction of **4** with fluoride, a typical S_NAr mechanism is found, whether attack of F^- occurs on C(1) (sydnone-bearing) or C(4) (nitro-bearing). In both cases, a barely stable Meisenheimer σ-complex (**int**) is located after the rate-determining fluoride addition transition state (**TS1**). Addition at C(1) is predicted to be 3.9 kcal/mol more favorable than addition at C(4), which is consistent with exclusive substitution of the sydnone group from **4**.

This reactivity difference can be explained by the electronic structure of **4**. Natural bond orbital (NBO) analysis shows that C(1) bears a partial positive charge (+0.18) double in magnitude to that of C(4) (+0.07).[19b] This indicates that a sydnone is inductively more electron-withdrawing than a nitro. This also explains why the formation of **4a** is more exergonic (by 10.0 kcal/mol) than **4b**, following the elimination transition state (**TS2**). Indeed, the sydnone anion ejected upon C(1) substitution is an excellent leaving group, much more stable than the nitrite that would result from reaction at C(4).[19b]

Although a sydnone is inductively more electron-withdrawing than a nitro, it cannot however achieve full resonance with the aromatic ring, due to unfavorable *peri* hydrogen contacts that prohibit the two groups from being coplanar. In **4**, the sydnone plane lies 40° away from the aryl plane (Figure 1), limiting its ability to stabilize an incoming negative charge by resonance delocalization. As such, we have estimated the Hammett σ^-_p constant[21] of sydnone (0.79)[22] to be much smaller than that of nitro (1.24).[19b] This indicates that a nitro is a better anion stabilizer than a sydnone, and its positioning *para* to the site of attack is preferred during an S_NAr reaction. Overall, fluoride addition at C(1) of **4** is strongly favored because this pathway enjoys greater stabilizing interactions as the reaction progresses. This was confirmed by a distortion/interaction analysis along the IRC.[19b, 23]

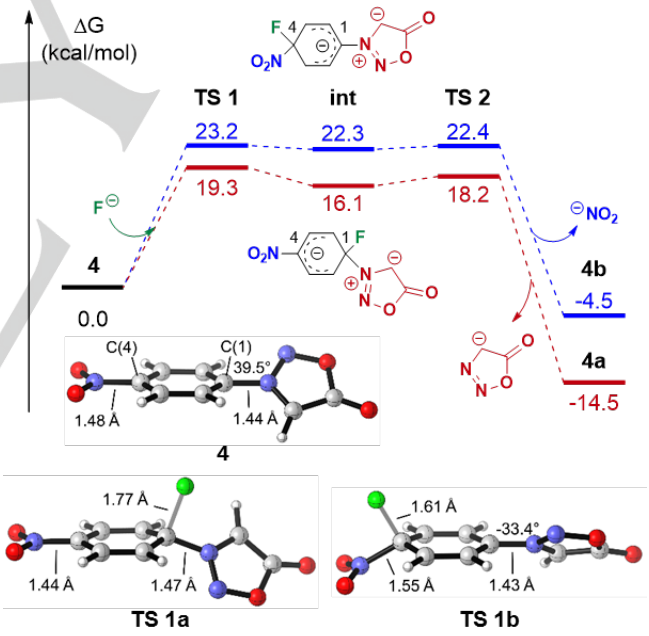


Figure 1. Calculated free energy profile for addition of fluoride to either C(1) (pathway a, in red) or C(4) (pathway b, in blue) of **4** (M06-2X/6-311+G(d,p)/SMD(DMSO) level of theory).

With these results in hand, the optimized reaction conditions were applied to a series of diverse *N*-arylsydnones to establish the scope of the reaction. As summarized in Figure 2, the radiofluorination proceeds in high RCC with substrates bearing electron-withdrawing substituents on the aryl ring and is compatible with numerous functional groups, such as nitro, cyano, ester, chloro, trifluoromethyl, ether, sulfone, sulfonamide,

pyrrolidinyl, morpholinyl and amide. Several heterocycles, which are often problematic for metal-mediated radiofluorination methods, underwent radiofluorination with high RCC to afford thiophene (**15a**), benzofuran (**16a**) and pyridine (**17a**) derivatives. Of particular note is the successful preparation of ethyl 3-[^{18}F]fluorobenzofuran-2-carboxylate **16a** in 45% RCC which is, to the best of our knowledge, the first report of an [^{18}F]benzofuran derivative. Synthesis of methyl 3-[^{18}F]fluorothiophene-2-carboxylate **15a** in 33% RCC is also significant as thiophenes are consistently difficult to radiofluorinate.[4] Unactivated or electron rich substituents failed to give detectable [^{18}F]fluorinated products. [19b]

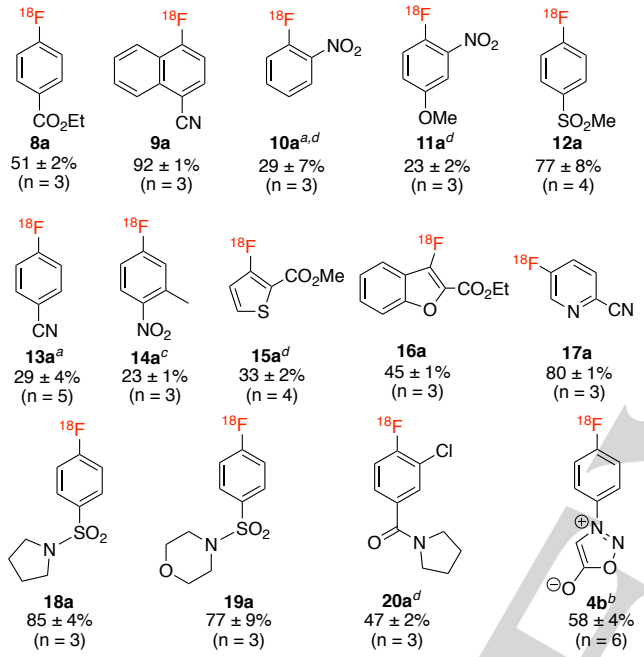
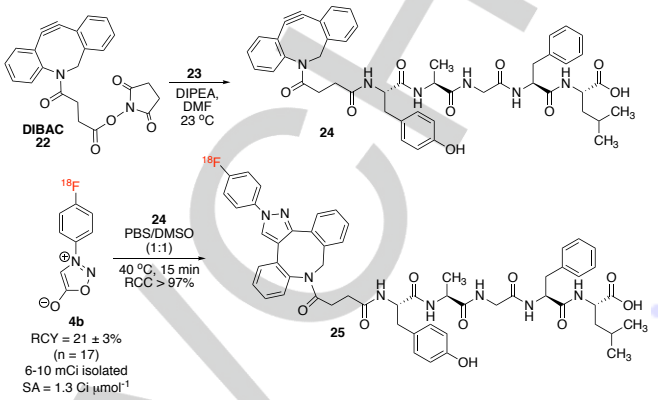


Figure 2. Scope of sydnone-mediated ^{18}F fluorination. Reaction conditions: precursor (25 μmol), Et_4NHCO_3 (50 μmol), DMSO (200 μL), [^{18}F]fluoride (300 μCi), 150 °C, 5 min. RCC was determined by radio-TLC. The identity of each labeled product was confirmed by radio-HPLC; [a]10 min. [b]15 min. [c]20 min. [d]RCC reported as radio-TLC conversion multiplied by radio-HPLC fraction of identified product.

While sydnones are valuable precursors for the synthesis of functionalized pyrazoles[24] and biologically interesting molecules,[16c] their most popular utility in the last few years has been their role in bioorthogonal reactions.[17b, 25] Previously, we disclosed the bioorthogonal reaction of phenyl sydnones with dibenzocyclooctyne derivatives DIBAC and BARAC to undergo [3+2] cycloaddition for applications in fluorescence protein labeling.[25c] Encouraged by these results, we sought to utilize this ligation to rapidly incorporate [^{18}F]fluorine into peptides and other biomolecules for applications in PET molecular imaging. Thus, we applied our radiofluorination method towards the synthesis of 4-[^{18}F]fluorophenyl sydnone **4b** via the phenyl bissydnone precursor **21** and optimized the fully automated process using an ELIXYS radiosynthesis module (Tables S3 and S4). Unlike prosthetic groups such as [^{18}F]fluoroethylazide and PEGylated counterparts,[26] sydnone **4b** is stable, non-volatile and displays strong UV absorbance. These properties make isolation and handling significantly less challenging and also simplify identification and quantification of the radiolabeled product via HPLC analysis.



Scheme 4. Preparation and application of [^{18}F]sydnone **4b** towards ^{18}F labelling of peptide [D-Ala^2, D-Leu^5]-Enkephalin **23**.

Using **4b** as a prosthetic group, we radiolabeled the 5 amino acid (H-Tyr-Ala-Gly-Phe-Leu-OH) neuropeptide, [D-Ala^2, D-Leu^5]-Enkephalin **23** (Scheme 4). Peptide **23** is a selective delta-opioid receptor agonist which displays protective effects towards the preservation of neurologic function and neuronal damage against hypoxic or ischemic induced brain injury.[27] Peptide **23** was functionalized with succinimidyl ester **22** to afford DIBAC-peptide conjugate **24**. The desired 4-[^{18}F]fluorophenyl sydnone **4b** (6-10 mCi) was purified and isolated within 62 min from the end of bombardment in 21 ± 3% non-decay-corrected radiochemical yield (RCY) (n=17) with a specific activity of 1.3 Ci μmol^{-1}. Purified **4b** was stirred with **24** in 1:1 DMSO:PBS at a concentration typically reported for [^{18}F]peptide labeling.[28] Remarkably, clean conversion (>97%) to pyrazole **25** was observed after 15 min at 40 °C, as determined by HPLC analysis of the reaction mixture (Figures S24 and S25) Notably, in all cases investigated, cycloaddition with **4b** proceeded at 37 °C to >98% conversion after 30 min; at 50 °C, complete conversion was achieved within 8 min (Table S6).[19b] Our application of [^{18}F]sydnones as bioorthogonal prosthetic groups for the production of ^{18}F radiotracers is related to Taran and coworkers' recent Pd(II)-mediated formation of 4-[^{18}F]fluoro-*N*-(*p*-tolyl)-sydnone, which is also an efficient cycloaddition partner.[29] Indeed, our method compares advantageously as it uses simple reagents for one-step, direct radiofluorination without transition metals, gives improved RCY and is fully automatable.

In conclusion, the first practical nucleophilic radiofluorination of anilines with [^{18}F]fluoride is achieved by the initial modification of $ArNH_2$ to an *N*-arylsydnone precursor via a two-step process. This simple transformation was successfully automated on a commercial radiochemistry synthesis module to provide an efficient synthesis of 4-[^{18}F]fluorophenyl sydnone which was utilized to prepare an ^{18}F-labeled neuropeptide via bioorthogonal cycloaddition. We anticipate this methodology will

complement the expanding radiofluorination methods and, due to its operational simplicity, find extensive applications in the production of radiopharmaceuticals for PET molecular imaging.

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Keywords: fluorine-18 • fluoroarene • sydnone • click chemistry • peptide radiolabeling

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Entry for the Table of Contents

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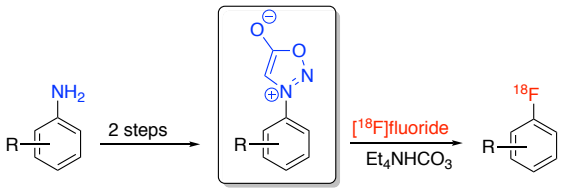

A practical radiofluorination of anilines with [^{18}F]fluoride is achieved via *N*-arylsydnone intermediates. This method displays broad functional group tolerance, is compatible to automation on a commercial radiosynthesis module and can facilitate rapid ^{18}F-labeling of peptides.

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Page No. – Page No.

Synthesis of [^{18}F]Fluoroarenes via Nucleophilic Radiofluorination of *N*-Arylsydnones